Official Title: A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Efficacy of INCB001158 in Combination With Chemotherapy, in Subjects With Advanced or Metastatic Solid Tumors

NCT Number: NCT03314935

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Clinical Study Protocol

INCB 01158-203

A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Efficacy of INCB001158 in Combination With Chemotherapy, in Subjects With Advanced or Metastatic Solid Tumors

Product:	**INCB001158**
IND Number:	[redacted]
EudraCT Number:	**2017-002904-29**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**07 AUG 2017**
Protocol Amendment (Version) 1:	**31 OCT 2017**
Protocol Amendment (Version) 2:	**27 SEP 2018**
Protocol Amendment (Version) 3:	**17 MAY 2019**
Protocol Amendment (Version) 4:	**09 DEC 2020**

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 01158-203 Protocol Amendment 4 (Version 4 dated 09 DEC 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: A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Efficacy of INCB001158 in Combination With Chemotherapy, in Subjects With Advanced or Metastatic Solid Tumors

Protocol Number: INCB 01158-203	**Study Phase:** 1/2

Indication:

Phase 1: advanced or metastatic solid tumors

Phase 2: advanced/metastatic microsatellite stable colorectal cancer (MSS-CRC), biliary tract cancer (BTC), gastroesophageal cancer (GC), and endometrial cancer (EC) and recurrent ovarian cancer (OC)

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• **Phase 1:** To assess the safety and tolerability and determine the recommended Phase 2 dose (RP2D) of INCB001158 in combination with chemotherapy.	• Safety, tolerability, dose-limiting toxicities (DLTs), and RP2D of INCB001158 in combination with chemotherapy, as assessed by adverse events (AEs), clinical laboratory tests, physical examination results, and 12-lead electrocardiogram (ECG) results.
• **Phase 2:** To evaluate the objective response rate (ORR) of INCB001158 in combination with chemotherapy.	• ORR, defined as the percentage of subjects having a complete response (CR) or partial response (PR), as determined by investigator assessment of radiographic disease as per RECIST v1.1.
Secondary	
• **Phase 2:** To assess the safety, tolerability, and RP2D of INCB001158 in combination with chemotherapy.	• Safety, tolerability, and RP2D of INCB001158 in combination with chemotherapy, as assessed by AEs, clinical laboratory tests, physical examination results, and 12-lead ECG results.
• To evaluate the antitumor effect of INCB001158 in combination with chemotherapy.	• ORR, defined as the percentage of subjects having a CR or PR, as determined by investigator assessment of radiographic disease as per RECIST v1.1 (Phase 1 only). • Duration of response (DOR), defined as the time from earliest date of CR or PR (as determined by investigator assessment of radiographic disease assessment per RECIST v1.1) until the earliest date of disease progression or death due to any cause, if occurring sooner than disease progression. • Disease control rate (DCR), defined as the percentage of subjects having CR, PR, or stable disease (SD) for at least 8 weeks, as determined by investigator assessment of radiographic disease as per RECIST v1.1. • Progression-free survival (PFS), defined as the time from the date of first dose of study drug until the earliest date of disease progression (as determined by investigator assessment of radiographic disease assessment per RECIST v1.1), or death due to any cause, if occurring sooner than progression.

• To determine the pharmacokinetics (PK) of INCB001158 in subjects treated with INCB001158 in combination with chemotherapy.	• PK of INCB001158 will be assessed by summarizing C_{min}, C_{max}, t_{max}, AUC_{0-t}, and $AUC_{0-\tau}$.

[redacted]

Overall Study Design: This is an open-label, nonrandomized, Phase 1/2 study to evaluate the safety, tolerability, and antitumor activity of INCB001158 in combination with 3 different chemotherapy regimens. Phase 1 will consist of dose-escalation using a Bayesian Optimal Interval (BOIN) design and will determine the RP2D of INCB001158 when given in combination with each chemotherapy regimen; efficacy will also be explored. Subjects with advanced or metastatic solid tumors for whom treatment with one of the chemotherapy regimens is appropriate will be enrolled in Phase 1. Phase 2 will evaluate ORRs using a Simon 2-stage design to determine whether the combinations have sufficient antitumor activity to warrant further testing in subsequent clinical studies and will further evaluate the safety and tolerability of the RP2D of INCB001158 when given in combination with chemotherapy. Subjects with advanced or metastatic CRC, BTC, OC, GC, and EC will be enrolled in the Phase 2 expansion cohorts.

Phase 1 Dose Escalation

In Phase 1, a BOIN design will be used to determine the RP2D of the combination of INCB001158 and chemotherapy in 21-day (for gemcitabine/cisplatin) or 28-day (for mFOLFOX6 or paclitaxel) treatment cycles in subjects with advanced or metastatic solid tumors. The RP2D will then be further assessed in tumor expansion cohorts in Phase 2.

Subjects with advanced or metastatic solid tumors will be assigned to 1 of the treatment groups summarized below based on the chemotherapy regimen most appropriate for the subject's tumor type.

Treatment Group A	**INCB001158**	**mFOLFOX6**
	25-150 mg PO BID continuous daily dosing	Oxaliplatin 85 mg/m^2 IV on Day 1 and Day 15 of a 28-day cycle Leucovorin 400 mg/m^2 IV on Day 1 and Day 15 of a 28-day cycle 5-Fluorouracil 400 mg/m^2 IV bolus on Day 1, then 1200 mg/m^2 per day IV infusion over 46 hours for a total dose of 2400 mg/m^2 on Day 1 and Day 15 of a 28-day cycle
Treatment Group B	**INCB001158**	**Gemcitabine and cisplatin**
	25-150 mg PO BID continuous daily dosing	Gemcitabine 1000 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle Cisplatin 30 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle
Treatment Group C	**INCB001158**	**Paclitaxel**
	25-150 mg PO BID continuous daily dosing	Paclitaxel 80 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle

BID = twice daily; IV = intravenous; PO = orally.

Dose escalation will begin with starting doses of INCB001158 at least 2 dose levels below the maximum tolerated and tested dose from the INCB 01158-101 study (likely to be 50 mg BID or 75 mg BID – see Table below, column A and B, respectively.

The doses of INCB001158 to be evaluated and scenarios for dose escalation and de-escalation are summarized below:

INCB001158 Dose Cohort	INCB001158 Dose Levels for Phase 1	
	A. Starting Dose of 50 mg BID	**B. Starting Dose of 75 mg BID**
-1	25 mg BID	50 mg BID
1 (starting dose)	**50 mg BID[a]**	**75 mg BID[b]**
2	75 mg BID	100 mg BID
3	100 mg BID	150 mg BID
4	150 mg BID	N/A

BID = twice daily.
[a] If INCB001158 50 mg BID is not tolerated within a treatment group, INCB001158 25 mg BID may be evaluated.
[b] If INCB001158 75 mg BID is not tolerated within a treatment group, INCB001158 50 mg BID may be evaluated.

If the starting dose is not 1 of those 2 dose levels, dose escalation will follow the same pattern, and the exact dose escalation table will be provided to sites. The INCB001158 dose will be escalated using an open-label BOIN design in each chemotherapy regimen, and a pharmacologically active dose (PAD) or the maximum tolerated dose (MTD) will be determined, or the maximum dose of INCB001158 (150 mg BID) will be reached. A PAD of INCB001158 is defined as a dose that achieves a trough (C_{min}) plasma concentration of INCB001158 at steady state of ≥ 1 μM that is equivalent to the IC_{90} for arginase 1. This definition may be modified based on emerging data from the INCB 01158-101 first-in-human study, upon agreement between the medical monitor and the study investigators. The MTD is the maximum tolerated or tested dose of INCB001158, such that fewer than 33% of the subjects receiving the combination experience a DLT during the first 28 days on study drug. After the dose escalation is completed, one of the INCB001158 dose levels that is pharmacologically active and tolerable in combination with each chemotherapy regimen (ie, MTD or lower), will be the RP2D.

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

Phase 2: Expansion Cohorts

To determine whether the combinations result in adequate ORRs to warrant further testing in subsequent clinical studies, a Simon 2-stage design will be used for each tumor expansion cohort to evaluate the ORR of the RP2D of INCB001158 determined in Phase 1 in combination with chemotherapy and further evaluate the safety and tolerability of the combination. If, at the time of completion of enrollment in Stage 1, it is not known whether the target ORR to proceed to Stage 2 will be met, then enrollment will be paused until and unless the ORR to proceed has been met.

Enrollment in a specific expansion cohort will begin when the RP2D of INCB001158 for the corresponding treatment group in Phase 1 has been determined.

The expansion cohorts will be limited to the following advanced/metastatic or recurrent tumor types:

- Cohort A1: CRC (INCB001158 + mFOLFOX6)
- Cohort B1: BTC (INCB001158 + gemcitabine/cisplatin)
- Cohort B2: OC (INCB001158 + gemcitabine/cisplatin)
- Cohort C1: GC (INCB001158 + paclitaxel)
- Cohort C2: EC (INCB001158 + paclitaxel)
- Cohort C3: OC (INCB001158 + paclitaxel)

Subjects will be assigned to the expansion cohorts summarized below based on the chemotherapy regimen most appropriate for the subject's tumor type:

Expansion Cohort A1	**INCB001158**	**mFOLFOX6**
	PO BID continuous daily dosing	Oxaliplatin 85 mg/m^2 IV on Day 1 and Day 15 of a 28-day cycle Leucovorin 400 mg/m^2 IV on Day 1 and Day 15 of a 28-day cycle 5-Fluorouracil 400 mg/m^2 IV bolus on Day 1, then 1200 mg/m^2 per day IV infusion over 46 hours for a total dose of 2400 mg/m^2 on Day 1 and Day 15 of a 28-day cycle
Expansion Cohort B1	**INCB001158**	**Gemcitabine and Cisplatin**
	PO BID continuous daily dosing	Gemcitabine 1000 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle Cisplatin 25 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle
Expansion Cohort B2	**INCB001158**	**Gemcitabine and Cisplatin**
	PO BID continuous daily dosing	Gemcitabine 750 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle Cisplatin 30 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle
Expansion Cohorts C1, C2, and C3	**INCB001158**	**Paclitaxel**
	PO BID continuous daily dosing	Paclitaxel 80 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle

BID = twice daily; IV = intravenous; PO = orally.

Continuous evaluation of toxicity events will be performed in the expansion cohorts. If the cumulative incidence of ≥ Grade 3 INCB001158-related AEs or ≥ Grade 3 chemotherapy-related AEs is > 40% after 10 subjects are enrolled in a specific expansion cohort within Phase 2, then further enrollment in that cohort will be interrupted until the sponsor and investigators determine the appropriate course of action. If an expansion cohort is discontinued due to toxicity, a new cohort may be initiated at a previously tested lower dose level.

[redacted]

Study Population:

Phase 1 Dose Escalation: Subjects with previously treated advanced solid tumors who have progressed on or were either ineligible or intolerant to standard anti-cancer therapy will be enrolled.

Phase 2 Expansion Cohorts: Subjects with histologically or cytologically confirmed advanced or metastatic MSS-CRC, BTC, OC, GC, and EC.

Key Inclusion Criteria:

- Men or women aged 18 years or older.
- Presence of measurable disease per RECIST v1.1.
  Note: If subjects have only 1 measurable lesion per RECIST v1.1, this lesion should not have been in the field of prior irradiation unless there is documented progression of the lesion(s).
- ECOG performance status 0 to 1.
- [redacted]
- Willingness to undergo pretreatment and on-treatment tumor biopsies, until at least 5 evaluable paired specimens are collected in each cohort.
- Have resolution of all toxicities and any toxic effect(s) of the most recent prior therapy to Grade 1 or less (except alopecia).
- Adequate renal, hepatic, and hematologic functions as defined by laboratory parameters within ≤ 7 days before treatment initiation.
  - Absolute neutrophil count ≥ 1.5×10^9/L.
  - Platelets ≥ 100×10^9/L.
  - Hemoglobin ≥ 9 g/dL.
  - Measured or calculated creatinine clearance (glomerular filtration rate can also be used in place of creatinine or creatinine clearance) ≥ 50 mL/min.
    Note: Creatinine clearance should be calculated per institutional standard.
  - Total bilirubin ≤ 1.5 × upper limit of normal (ULN) OR direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 × ULN.
  - If there is no institutional normal range available for the direct bilirubin, the direct bilirubin should be < 40% of the total bilirubin.
  - In no case can total bilirubin exceed 3.0 × ULN.
  - Aspartate aminotransferase (serum glutamic oxaloacetic transaminase) and alanine aminotransferase (serum glutamic pyruvic transaminase) ≤ 2.5 × ULN.
  - International normalized ratio (INR) or prothrombin time (PT) ≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or INR is within therapeutic range of intended use of anticoagulants.
  - Activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy, as long as aPTT is within therapeutic range of intended use of anticoagulants.
- Albumin > 3.0 g/dL.
- <u>Phase 1 dose escalation only</u>
  - Subjects with histologically or cytologically confirmed advanced or metastatic solid tumors that have failed prior standard therapy (disease progression, subject refusal, or intolerance is also allowable).
    Note: There is no limit to the number of prior treatment regimens.
  - Locally advanced disease must not be amenable to resection with curative intent.

- Phase 2 Expansion Cohort A1: MSS-CRC subjects only
  - Subjects with histologically or cytologically confirmed advanced or metastatic adenocarcinoma of the colon or rectum.
    Note: Should have documented microsatellite stable (MSS) status, or consent to local institutional microsatellite instability (MSI) testing during the screening period.
    Note: Must have received at least 1, but not more than 2, prior chemotherapy regimens for locally advanced/metastatic CRC, including fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy; with or without anti-vascular endothelial growth factor therapy (if no contraindication).
    Note: Subjects who completed a fluoropyrimidine-, irinotecan-, or oxaliplatin-based chemotherapy regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy and progressed ≥ 6 months after completing therapy will be eligible. If progression occurred < 6 months after completing therapy, then the subject will not be eligible.
- Phase 2 Expansion Cohort B1: BTC subjects only
  - Subjects with histologically or cytologically confirmed nonresectable advanced or metastatic BTC (intra- or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma).
    Note: Should not have received prior systemic chemotherapy for metastatic or inoperable locally advanced BTC (not including adjuvant therapy completed at least 6 months prior to enrollment).
- Phase 2 Expansion Cohort B2: OC subjects only
  - Subjects with histologically confirmed recurrent epithelial ovarian, peritoneal, or fallopian tube carcinoma and carcinosarcomas (Sertoli-Leydig or germ cell cancers are excluded) that have progressed within 6 months of prior cytotoxic chemotherapy.
    Note: Should have received at least 1 and no more than 4 prior therapies, and failed at least 1 standard line of chemotherapy.
    Note: Adjuvant regimens given within 6 months of screening would be counted as first-line therapy.
- Phase 2 Expansion Cohort C1: GC subjects only
  - Subjects with histologically or cytologically confirmed advanced or metastatic adenocarcinoma of the stomach, esophagus, or gastroesophageal junction.
    Note: Should have received only 1 prior chemotherapy regimen for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy). Adjuvant regimens given within 6 months of screening would be counted as first-line therapy.
- Phase 2 Expansion Cohort C2: EC subjects only
  - Subjects with histologically or cytologically confirmed advanced or metastatic endometrial carcinoma.
    Note: Should have documented MSI status (eg, MSI-high, MSI-low, MSS), or consent to local institutional MSI testing during the screening period.
    Note: Should have received at least 1, but not more than 2, prior chemotherapy regimens for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy). Adjuvant regimens given within 6 months of screening would be counted as first-line therapy.
    Note: May have received prior hormonal and/or biological therapy in addition to prior systemic chemotherapy, which will not count as prior therapy.
- Phase 2 Expansion Cohort C3: OC subjects only
  - Subjects with histologically confirmed recurrent epithelial ovarian, peritoneal or fallopian tube carcinoma and carcinosarcomas that have progressed within 6 months of prior cytotoxic chemotherapy (Sertoli-Leydig or germ cell cancers are excluded).
    Note: Should have received no more than 5 prior therapies and failed at least 1 standard (platinum-containing) chemotherapy regimen and be considered platinum resistant.
    Note: Adjuvant regimens given within 6 months of screening would be counted as first-line therapy.

Key Exclusion Criteria:

- Participation in any other study in which receipt of an investigational study drug or device occurred within 28 days or 5 half-lives (whichever is longer) before first dose. For investigational agents with long half-lives (eg, 5 days), enrollment before the fifth half-life requires medical monitor approval.
- Has received a prior monoclonal antibody within 4 weeks or 5 half-lives (whichever is shorter) before administration of study drug.
  - Exception: Washout of immune checkpoint inhibitor therapy is NOT required.
  - Exception: Denosumab may be used.
- Has had prior chemotherapy or targeted small molecule therapy within 2 weeks before administration of study treatment.
- Has received prior approved radiotherapy within 14 days of study therapy (exception for radiation to central nervous system [CNS], which requires ≥ 28-day washout as described below).
  Note: Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiation therapy) to non-CNS disease
- Subjects must not have received therapy with an arginase inhibitor.
  Note: Prior immunotherapy treatment with an anti–programmed death-1 receptor, anti–programmed death-1 receptor ligand, anti–programmed death-2 receptor ligand, anti–cytotoxic T-lymphocyte–associated protein 4, anti-CD137, or any other antibody or drug specifically targeting immune checkpoint pathways is allowed.
- Has had major surgery within 4 weeks before enrollment (C1D1).
- Has had known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 2 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy, or cancers from which the subject has been disease-free for > 1 year, after treatment with curative intent.
- Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (exceeding 10 mg daily of prednisone equivalent in dose) or any other form of immunosuppressive therapy within 7 days before the first dose of study treatment.
- Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
  Note: Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
- Has a known history of human immunodeficiency virus (HIV) infection. HIV testing is not required unless mandated by the local health authority.
- Has a known history of or is positive for hepatitis B (hepatitis B surface antigen [HBsAg] reactive) or hepatitis C.
  Note: Testing must be performed to determine eligibility.
  - Hepatitis B virus DNA must be undetectable and HBsAg negative at screening visit.
  - Hepatitis C antibody testing is allowed for screening purposes in countries where hepatitis C virus (HCV) RNA is not part of standard-of-care treatment. In these cases, HCV antibody-positive patients will be excluded.
  - Subjects who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at screening visit.
- Has known active CNS metastases and/or carcinomatous meningitis.
  Note: Subjects with previously treated brain metastases may participate provided that they are stable (without evidence of progression by imaging for at least 28 days before the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or cerebral edema, and have not required steroids for at least 14 days before the first dose of study drug.

Note: Subjects with evidence of cerebral edema or those with < 28 days since radiation therapy to the CNS will be excluded from study.

- Has not recovered to ≤ Grade 1 from toxic effects of previous therapy and/or complications from previous surgical intervention before starting study therapy.
  Note: Subjects with stable chronic AEs (≤ Grade 2) not expected to resolve (eg, alopecia) are exceptions and may enroll.
  Note: Subjects with a history of peripheral neuropathy ≥ Grade 2 will be excluded.
- Has a known or suspected defect in the function of the urea cycle, including a known deficiency of carbamoyl phosphate synthetase I, ornithine transcarbamylase, argininosuccinate synthetase, argininosuccinate lyase, N-acetyl glutamate synthetase, or arginase.
- Evidence of interstitial lung disease or active, noninfectious pneumonitis.
- Inability to swallow food or any condition of the upper gastrointestinal tract that precludes administration of oral medications.
- Active infection requiring systemic therapy.
- Has known hypersensitivity to any of the active substances or any of their excipients, including mannitol.
- Women who are pregnant or breastfeeding.

INCB001158, Dosage, and Mode of Administration:

In Phase 1 dose escalation, INCB001158 will be administrated PO BID with the dose corresponding to cohort assignment. In Phase 2 expansion cohorts, INCB001158 will be administrated PO BID at the RP2D determined in the dose escalation as long as the subject is deriving benefit and has not met any of the Protocol-defined conditions for treatment withdrawal.

INCB001158 will be administrated PO BID in 28- or 21-day cycles depending on the chemotherapy regimens.

Chemotherapies, Dosage, and Mode of Administration:

5-Fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) will be administered on Day 1 and Day 15 of each 28-day cycle. Subjects will receive oxaliplatin 85 mg/m^2 IV concurrently with leucovorin 400 mg/m^2 IV over 2 hours (± 15 minutes), followed by a 5-fluorouracil 400 mg/m^2 IV bolus (administration time per institutional practice), then 1200 mg/m^2 per day IV continuous infusion over 46 hours for a total dose of 2400 mg/m^2. Investigators may reduce or discontinue oxaliplatin for peripheral neuropathy; if discontinued, investigators have the option to discontinue 5-fluorouracil and leucovorin. Subjects may receive prophylactic granulocyte-colony stimulating factor (G-CSF) support after completion of Cycle 1.

Gemcitabine and cisplatin will be administered on Day 1 and Day 8 of a 21-day cycle. For Phase 1 dose escalation, subjects with advanced or metastatic disease will receive gemcitabine 1000 mg/m^2 IV over 30 minutes (± 5 min) and cisplatin 30 mg/m^2 IV over 30 minutes (± 5 min) on Days 1 and 8 of each 21-day cycle. For Phase 2 tumor expansion, subjects will receive the gemcitabine/cisplatin regimen that is the standard dose and schedule used for the corresponding tumor type patients:

- In Cohort B1 (BTC), subjects will receive gemcitabine 1000 mg/m^2 IV over 30 minutes (± 5 min) and cisplatin 25 mg/m^2 IV over 30 minutes (± 5 min) on Days 1 and 8 of each 21-day cycle.
- In Cohort B2 (OC), subjects will receive gemcitabine 750 mg/m^2 IV over 30 minutes (± 5 min) and cisplatin 30 mg/m^2 IV over 30 minutes (± 5 min) on Days 1 and 8 of each 21-day cycle.

Subjects may receive prophylactic G-CSF support after completion of Cycle 1.

Paclitaxel will be administrated weekly at 80 mg/m^2 IV infusion over 1 hour (± 10 minutes), on Days 1, 8, and 15 of a 28-day cycle.

Study Schedule/Procedures:

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

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

Treatment:

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

All other treatment cycles: Day 1, Day 8, and Day 15 (± 3 days).

NOTE: As of Protocol Amendment 4, the only safety data that will be collected will be related to SAEs, AESIs, and pregnancy.

Efficacy assessments: Every 8 weeks (± 7 days).

NOTE: As of Protocol Amendment 4, no further efficacy assessments will be required beyond Week 96. Imaging should continue per standard of care after Week 96.

End of treatment: + 7 days of discontinuing treatment.

Safety follow-up: 30 days and 90 days (± 7 days) after end of treatment (or last dose of study drug if the end-of-treatment visit was not performed). These follow-up visits may be completed remotely (such as by televisit).

Disease status follow-up: Subjects who discontinue 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 (± 7 days) until a new cancer therapy is started, disease progression, death, or the end of the study.

NOTE: As of Protocol Amendment 4, no further disease status follow-up assessments will be required beyond the last safety follow-up visit.

[redacted]

Estimated Duration of Participation:

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

Estimated Number of Subjects:

Up to a total of 222 subjects (if starting dose level is 75 mg in Phase 1) or up to a total of 249 (if starting dose level is 50 mg in Phase 1) are planned for enrollment.

- Phase 1 dose escalation – Up to 87 (if starting dose level is 75 mg in Phase 1) or up to 114 (if starting dose level is 50 mg in Phase 1) evaluable subjects.
- Phase 2 tumor expansion (Simon 2-stage) – Approximately 55 to 135 evaluable subjects.

Coordinating Principal Investigator: TBD

Statistical Methods:

Sample Size Method: In Phase 1, the BOIN design will be used to determine the RP2D of INCB001158 given in combination with each chemotherapy regimen, in subjects with advanced or metastatic solid tumors. Dose escalation and de-escalation will follow the BOIN design algorithm. In

Phase 2, the sample size for each tumor type within a treatment group will be guided by the Simon 2-stage design.

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

Phase 2: Simon 2-Stage Design

Cohort (Tumor Type)	Background ORR	Target ORR	Alpha	Power	N for Stage 1	ORR to Proceed	N for Stage 2	ORR for Positive Cohort
A1 (MSS-CRC)	10%	30%	0.1	80	7	≥ 1/7	11	≥ 4/18
B1 (BTC)	20%	40%	0.1	80	12	≥ 3/12	13	≥ 8/25
B2 (OC)	15%	35%	0.1	80	9	≥ 2/9	14	≥ 6/23
C1 (GC)	15%	35%	0.1	80	9	≥ 2/9	14	≥ 6/23
C2 (EC)	15%	35%	0.1	80	9	≥ 2/9	14	≥ 6/23
C3 (OC)	15%	35%	0.1	80	9	≥ 2/9	14	≥ 6/23

Primary Analysis:

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

- Phase 1: Safety/tolerability/DLTs/RP2D, in all patients receiving at least 1 dose of study drug (safety population), as assessed by AEs, clinical laboratory assessments (including urine orotic acid), physical examination results, and 12-lead ECG results.
- Phase 2: ORR, defined as the percentage of subjects having a CR or PR, as determined by investigator assessment of radiographic disease as per RECIST v1.1 will be summarized for by expansion cohort.

Secondary Analyses:

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

- Phase 2: Safety/tolerability/DLTs/RP2D, in all patients receiving at least 1 dose of study drug (safety population), as assessed by AEs, clinical laboratory assessments (including urine orotic acid), physical examination results, and 12-lead ECG results.
- ORR, defined as the percentage of subjects having a CR or PR, as determined by investigator assessment of radiographic disease as per RECIST v1.1 (Phase 1 only).
- DOR, defined as the time from earliest date of CR or PR until the earliest date of disease progression per RECIST v1.1 or death due to any cause, if occurring sooner than progression.
- DCR, defined as the percentage of subjects having CR, PR, or SD for at least 8 weeks, as determined by investigator assessment of radiographic disease as per RECIST v1.1.
- PFS, defined as the time from date of first dose of study drug until the earliest date of disease progression (as determined by investigator assessment of objective radiographic disease assessments per RECIST v1.1) or death due to any cause, if occurring sooner than progression.

- The PK parameters of C_{max}, t_{max}, C_{min}, AUC_{0-t}, and $AUC_{0-\tau}$ (INCB001158) for first 12 subjects enrolled in Phase 2 will be calculated from the blood plasma concentrations of INCB001158 using standard noncompartmental (model independent) PK methods.

[redacted]

Interim Analysis:

In Phase 1, the BOIN design will be used to determine the RP2D of INCB001158 in combination with each chemotherapy regimen. To avoid assigning too many subjects to an overly toxic dose, we use the dose elimination rule when implementing the BOIN design. When ≥ 3 subjects have been treated, if the probability that the estimated toxicity rate that is above the target DLT rate is > 95% at a certain dose level, then this dose level and higher dose levels are assumed too toxic and will be eliminated.

In Phase 2, the Simon 2-stage design will be applied for each tumor within a given expansion cohort. During Stage 1, n_1 evaluable subjects treated at the recommended dose and schedule will be enrolled, and if r_1 or fewer responses are observed, then the cohort will be discontinued.

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

Abbreviation	Definition
5FU	5-fluoroucil
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BID	twice daily dosing
BOIN	Bayesian Optimal Interval
BTC	biliary tract cancer
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DKA	diabetic ketoacidosis
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EC	endometrial cancer
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
FOLFIRI	folinic acid, 5FU, and irinotecan
FOLFOX	folinic acid, 5FU, and oxaliplatin
mFOLFOX6	modified FOLFOX6
GC	gastroesophageal cancer
G-CSF	granulocyte-colony stimulating factor

Abbreviation	Definition
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
[redacted]	[redacted]
[redacted]	[redacted]
IEC	independent ethics committee
[redacted]	[redacted]
IN	Investigator Notification
INR	international normalized ratio
[redacted]	[redacted]
irAE	immune-related adverse event
IRB	institutional review board
[redacted]	[redacted]
IRT	interactive response technology
[redacted]	[redacted]
[redacted]	[redacted]
LFT	liver chemistry test
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
[redacted]	[redacted]
MSI-H	high microsatellite instability
MTD	maximum tolerated dose
MSI	microsatellite instability
MSS	microsatellite-stable
NCI	National Cancer Institute
NO	nitric oxide
NSCLC	non–small cell lung cancer

Abbreviation	Definition
OC	ovarian cancer
ORR	objective response rate
[redacted]	[redacted]
PAD	pharmacologically active dose
PD	progressive disease
PD-1	programmed death-1 receptor
PD-L1	programmed death-1 receptor ligand
PD-L2	programmed death-2 receptor ligand
PFS	progression-free survival
PK	pharmacokinetic
PO	orally
PR	partial response
PT	prothrombin time
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RT	radiation therapy
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
T1DM	Type 1 diabetes mellitus
TEAE	treatment-emergent adverse event
Tregs	regulatory T-cells
ULN	upper limit of normal
USPI	United States Package Insert
VEGF	vascular endothelial growth factor

1. INTRODUCTION

1.1. Background

1.1.1. Role of the Immune System in Cancer

Although the immune system can recognize and kill transformed cells, clinically evident tumors have evaded immune destruction through different immune escape mechanisms. A complex network of interacting mechanisms governs the establishment and maintenance of cancer-induced immunosuppression. Immunosuppression is mediated through production of anti-inflammatory mediators, induction of T-cell anergy, and recruitment of immunoregulatory cells, such as Tregs and tolerogenic myeloid populations. The promotion of suppressor cells and Tregs by tumors plays a central role in escape from immunosurveillance including induction of an immunosuppressive tumor microenvironment (Kumar et al 2016).

Targeting the immune system is a proven effective approach for the treatment of cancer, and immunotherapy is now an accepted standard of care in several tumor types. Immune checkpoint inhibitors targeting co-inhibitory receptors such as CTLA-4 and PD-1 provide a critical mechanism for restoring host immune response against the tumor (Chen and Mellman 2013).

Evasion of tumor cells from immune elimination represents a major obstacle in cancer immunotherapy. Although these agents have antitumor activity in patient subsets when administered as monotherapy, multiple immune inhibitory mechanisms are present concurrently within the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect (Quezada et al 2013).

1.1.2. Targeting Myeloid-Derived Suppressor Cells and Arginase in Cancer

Myeloid-derived suppressor cells are immunosuppressive cells that play a critical role in maintaining normal homeostasis but under chronic inflammatory conditions can skew the environment toward supporting tumor development and metastasis (Meirow et al 2015). The immunosuppressive tumor microenvironment is a key obstacle that has been described to hinder cancer immunity (Gabrilovich 2017). Solid tumors have been shown to have moderate to extensive infiltration of immunosuppressive myeloid cells (Messmer et al 2015, Solito et al 2014). MDSCs and neutrophils are present in multiple solid tumors and correlate with poor outcome (Gentles et al 2015). MDSCs have been shown to be significantly increased in cancer patients of all stages relative to healthy volunteers, with a significant correlation between circulating MDSC, metastatic burden, and clinical cancer stage (Diaz-Montero et al 2009). Therefore, MDSCs are considered new therapeutic targets for the treatment of cancer (Wesolowski et al 2013). MDSCs secrete anti-inflammatory cytokines and express immunosuppressive metabolic enzymes, such as arginase.

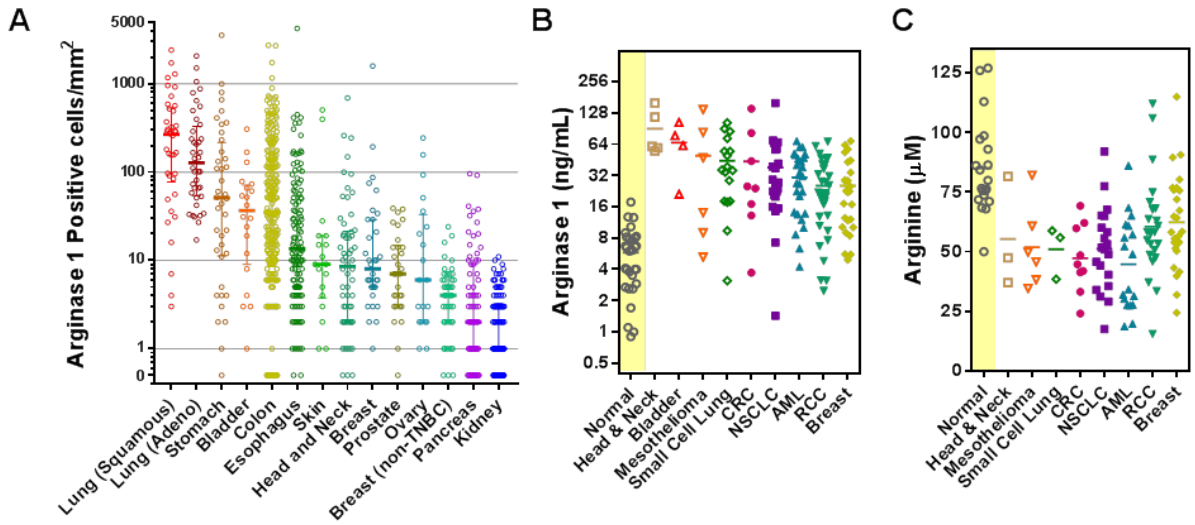
Arginase catalyzes the hydrolytic conversion of arginine to ornithine and urea. There are 2 arginase isoforms, arginase 1 and arginase 2, that catalyze the same chemical reaction but differ in terms of their regulation, subcellular localization, and cellular/tissue expression. Arginase 1 is a cytosolic enzyme primarily and abundantly found in liver hepatocytes, where it plays a crucial role in ammonia detoxification by catalyzing the final step of the urea cycle. A separate gene encodes arginase 2 (gene symbol: ARG2), a mitochondrial enzyme that is more widely expressed across cell types.

In the immune system, both granulocytic MDSCs and neutrophils contain the enzyme arginase 1 within secretory granules. Upon stimulation by factors within the tumor microenvironment (eg, pro-inflammatory cytokines, such as interleukin-8 [IL-8] and tumor necrosis factor-alpha [TNF-α]), arginase is released into the tumor microenvironment via degranulation, resulting in substantial local depletion of the amino acid arginine (Rotondo et al 2009, Raber et al 2012). Arginase-mediated arginine depletion is an effective way to control adaptive immune responses as adequate levels of arginine are crucial for T-cell proliferation and function (Munder 2009, Rodriguez et al 2007). Arginine itself is a critical factor in the proliferation and activation of cytotoxic T cells and natural killer cells. Antitumor activity has been reported in mice when arginase is knocked out in the myeloid lineage (Colegio et al 2014).

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 1 [A]). The positive arginase 1 IHC staining in tumor microarrays in this study was largely confined to polymorphonuclear cells based on morphology. Analysis of plasma from cancer patients across multiple histotypes demonstrated elevated arginase 1 protein levels and lower arginine levels compared with normal healthy control subjects (Figure 1 [B, C]).

[redacted]

Figure 1: Arginase and Arginine in Cancer Patients



[A] Frequency of arginase 1 expressing cells infiltrating human solid tumors. 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.

1.1.3. Overview of INCB001158

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

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

In cell-based assays, INCB001158 reversed the growth suppressive effects of human neutrophils on human T-cells when co-cultured *ex vivo* with an EC_{50} of 162 nM. Similarly, INCB001158 reversed inhibition of T-cell growth by patient-derived MDSCs with similar potency. In both cases, INCB001158 was able to antagonize the depletion of arginine mediated by neutrophils or MDSCs in a dose-dependent fashion. INCB001158 has no direct growth inhibitory or cytotoxic activity on tumor cells or on immune effector cells.

INCB001158 has single-agent and combination activity in syngeneic tumor models. Oral BID administration of single-agent INCB001158 produced a dose-dependent reduction in the growth of subcutaneously implanted LLC (lung) tumors. The efficacy of INCB001158 in LLC tumors is immune-mediated. When LLC tumors were grown in immuno-compromised severe combined immunodeficiency mice, there was no antitumor activity of INCB001158. The combination of INCB001158 with gemcitabine or paclitaxel in CT26 (colon), 4T1 (breast), LLC (lung) and paclitaxel plus anti–PD-L1 in B16-F10 (melanoma) tumor models resulted in enhanced antitumor activity. INCB001158 combinations with an IDO inhibitor and/or anti–PD-L1 also demonstrated antitumoral activity.

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

Refer to the IB for additional details of the INCB001158 preclinical experiments and updated data from the clinical study INCB 01158-101.

1.1.4. Overview of FOLFOX in Colorectal Cancer

CRC is the third most commonly diagnosed cancer and a leading cause of death worldwide. Patients with advanced or metastatic CRC receive combined chemotherapies, FOLFOX, and FOLFIRI as standard first-line treatment. There are several different FOLFOX regimens that differ in the doses and ways in which the 3 drugs are given, and the modified regimen (mFOLFOX6) utilizes infusional administration of 5-FU. The second-line therapy regimen usually includes agents that were not used in the first chemotherapy backbone (Van Cutsem et al 2016). Thus, FOLFOX treatment can be used in the second and third-line setting after failure of a 5-FU– or an irinotecan-based prior line treatment, producing an ORR of approximately 10% with a PFS of approximately 5 months in second line (Guglielmi et al 2007). The anti-EGFR bevacizumab is approved in combination with a fluoropyrimidine-based regimen and is an option to consider in the second-line treatment, as well as other anti-angiogenic compounds, such as aflibercept or ramucirumab. Studies with immune checkpoint inhibitors

reported ORRs in the range of 26% to 57% in refractory patients with MSI-H CRC compared to 0% to 5% in MSS-CRC, indicating the need to improve the ORRs in MSS-CRC patients (Boland and Ma 2017).

1.1.5. Overview of Gemcitabine/Cisplatin in Biliary Tract Cancer

BTC is a relatively uncommon cancer in developed countries with approximately 1200 new cases in the United Kingdom and 9000 new cases in the United States per year. Most patients present with locally advanced (nonresectable) or metastatic disease and recurrence is frequent, even when surgery is feasible. The median survival with best supportive care in randomized studies is between 2.5 and 4.5 months. Gemcitabine has been found to exhibit synergistic effects on cytotoxic activity *in vitro* and *in vivo* when combined with cisplatin. The combination of gemcitabine with cisplatin for the treatment of BTC was initially studied in small observational and retrospective studies and then established in the Phase 2 ABC-01 study. Based on the Phase 3 ABC-02 study, the gemcitabine-cisplatin combination therapy has been accepted as standard first-line chemotherapy treatment in patients with advanced BTC (Valle et al 2010). The median OS rate for the combination therapy group was 11.7 months compared with 8.1 months for gemcitabine alone, and median PFS was 8.0 months compared with 5.0 months, respectively. ORR was also higher in the gemcitabine-cisplatin group, and the combination therapy had an acceptable toxicity profile. The gemcitabine-oxaliplatin regimen used in other studies produced a median OS rate of 10 months and median PFS of 4.2 months (Fiteni et al 2014). ORRs of approximately 20% have been reported for gemcitabine-cisplatin as first-line treatment for patients with advanced BTC (Bridgewater et al 2016).

1.1.6. Overview of Gemcitabine/Cisplatin and Paclitaxel in Ovarian Cancer

Epithelial OC remains the most lethal gynecologic malignancy, with an overall 5-year survival rate of 45%. Nearly 80% of patients with advanced stage OC will have tumor progression, or more commonly a recurrence. The international standard for first-line treatment of advanced disease is surgery and a chemotherapy combination of a taxane (usually paclitaxel) and a platinum agent. The PFS has remained fairly constant at about 18 months. Platinum-resistant disease is defined as patients whose recurrence is documented within 6 months of platinum-based chemotherapy, and the prognosis is especially disappointing. Treatment of recurrent platinum-resistant ovarian and peritoneal cancers represents a therapeutic challenge, and response rates with single-agent chemotherapy have been in the 10% to 20% range (Kumar et al 2010).

Gemcitabine has been found to be active in women with primary and recurrent OC. The addition of gemcitabine to cisplatin may have synergistic tumoricidal activity among women with recurrent OC, and response rates were reported in the range of 16% to 70%; median progression-free intervals were 4 to 7 months, and response rates were in the range of 20% in platinum-resistant tumors (Eltabbakh et al 2016).

Paclitaxel is a front-line agent for OC chemotherapy, along with the platinum agents. Paclitaxel has been one of the most promising drugs to enter into clinical studies in the setting of cisplatin-refractory OC. Responses have been reported in both heavily and minimally pretreated OC patients (20%-37%), but myelotoxicity was found to be a major concern. The activity of paclitaxel in epithelial OC is dose-dependent, and a randomized study (Rosenberg et al 2002) has

shown reduced toxicity and similar efficacy with weekly administration compared with every 3 weeks. Weekly paclitaxel has response rate of 20% to 25% in platinum-resistant, recurrent, OC patients and is associated with a favorable toxicity profile. In a Phase 3 study comparing weekly paclitaxel 80 mg/m^2 to paclitaxel 175 mg/m^2 every 3 weeks, the ORRs were 27% and 16%, respectively (Osman et al 2016).

1.1.7. Overview of Paclitaxel in Gastroesophageal Cancer

Gastric cancer is the fifth most common cancer worldwide, with the highest incidence in East Asia. Most cases, especially in the United States and Europe, are diagnosed at a late stage after becoming metastatic. Patients with advanced disease have a poor prognosis, with a median OS of 10 to 12 months (Digklia et al 2016). Treatment options of metastatic disease are mostly restricted to cytotoxic chemotherapy, but even these are associated with poor outcomes. Although recent Phase 3 studies showed some benefit from chemotherapy regimens including docetaxel, capecitabine, irinotecan, cisplatin, and oxaliplatin (median OS and PFS in of approximately 5 months), there is no internationally accepted standard-of-care for second-line treatment (Bilici 2014). Despite the availability of trastuzumab for patients with human epidermal growth factor receptor 2–positive disease and the approval of the anti-VEGFR2 monoclonal antibody ramucirumab as a second-line therapy, there still remains a need for effective treatment options for advanced gastric cancer. Ramucirumab in combination with paclitaxel in second-line treatment of GC improved median OS (9.6 months vs 7.4 months) and PFS (4.4 months vs 2.9 months) compared with paclitaxel alone (Wilke et al 2014).

Paclitaxel and irinotecan are considered standard second-line treatments for metastatic GEJ and gastric adenocarcinoma patients following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapies (Hironaka et al 2013). Median OS was 9.5 months in subjects treated with weekly paclitaxel and 8.4 months in the irinotecan group, while response rates were 20.9% and 13.6%, respectively. Weekly paclitaxel produced a response rate of 7.3% in a Phase 3 study in subjects with gastric carcinoma or adenocarcinoma of the esophagogastric junction that had progressed after treatment with a fluoropyrimidine/platinum-containing regimen (Al-Batran et al 2017).

1.1.8. Overview of Paclitaxel in Endometrial Cancer

Endometrial cancer is the only gynecologic malignancy with a rising incidence and mortality (Longoria and Eskander 2015). At the time of diagnosis, 67% of women have disease confined to the uterus and an associated 5-year survival rate of 95%, whereas patients with metastatic or recurrent disease have a 5-year survival rate of 16% (Siegel et al 2016). The standard-of-care in first-line treatment of metastatic endometrial carcinoma is paclitaxel with carboplatin or cisplatin, with both regimens producing similar ORR (approximately 51%), PFS (median 8 to 13 months), and OS (median 12 to 15 months) rates. Women who progress on first-line cytotoxic chemotherapy have largely chemoresistant disease associated with poor prognosis, and there is currently no consensus on treatment in the second- and third-line settings (Colombo et al 2016). Studies of cytotoxic therapies used in the second-line setting have generally produced RRs of 15% or lower, and only paclitaxel has consistently shown a response rate above 20%. Studies with weekly paclitaxel as first-line and second-line treatment have reported anticancer activity with an acceptable toxicity profile in advanced EC. Modest ORRs ranging from 0% to 24.5% were reported with targeted agents such as angiogenesis inhibitors,

EGFR inhibitors, and mTOR inhibitors in patients with advanced stage and recurrent EC (Fleming et al 2015).

1.2. Study Rationale

1.2.1. Rationale for Combining INCB001158 With Chemotherapy

While chemotherapy has largely been thought to be immunosuppressive and exert its effect via direct cytotoxicity, there is an emerging body of evidence to suggest that some chemotherapies may influence an immune response in tumors via induction of immunogenic cell death, elimination of immunosuppressive cells, or sensitization of tumor cells to immune effector cells (Apetoh et al 2015). Certain chemotherapeutic agents improve host immune responses and even break immune tolerance. FOLFOX may induce a decrease in granulocytic MDSCs, high levels of which are associated with a poor prognosis (Kanterman et al 2014, Limagne et al 2016). Platinum agents have demonstrated immunogenic effects that can lead to immunogenic cell death, thereby stimulating the immune system. Gemcitabine and cyclophosphamide have been shown to improve antitumor immunity by depleting Tregs, inhibiting their suppressor function, and leading to peripheral T-cell proliferation and natural killer cell activities (Ghiringhelli et al 2007, Le and Jaffee 2012, Shevchenko et al 2013). Gemcitabine reduces granulocytic MDSCs but not monocytic MDSCs, and MDSC levels correlate with shorter survival in patients with pancreatic adenocarcinoma (Eriksson et al 2017, Gabitass et al 2011). Paclitaxel and 5-fluorouracil have been shown to kill MDSCs and restore antitumor activity of CD8+ T cells in experimental models (Sevko et al 2013, Apetoh et al 2011, Vincent et al 2010). Low dose paclitaxel can stimulate tumor-associated macrophage–mediated cytotoxic immune response in vivo (Park et al 2013). In summary, some standard chemotherapy agents can impact both the tumor and host immune system, which provide strong rationale for their combination with selective immunotherapeutic interventions (Bracci et al 2014, Hato et al 2014).

Given these findings, the combination of different types of chemotherapy with the arginase inhibitor INCB001158 is a rational choice, especially in patients with limited or suboptimal treatment options. It is, therefore, expected that arginase inhibitor agents used in combination with chemotherapy regimens, such as mFOLFOX6, gemcitabine/cisplatin, and paclitaxel, may result in greater immunomodulatory effects in the tumor microenvironment and thereby enhance the clinical benefit in subjects with advanced or metastatic solid tumors (Draghiciu et al 2015).

1.2.2. Rationale for Study Population

Subjects with previously treated advanced solid tumors who have progressed on or were either ineligible or intolerant to standard anticancer therapy will be enrolled in Phase 1.

In Phase 2, the tumor expansion cohorts were selected based on preclinical data and elevated numbers of arginase-positive cells and MDSC infiltrates in tumor tissues and blood (see Section 1.1.2). Therefore, combining the arginase inhibitor INCB001158 and chemotherapy may result in enhanced clinical benefit in subjects with advanced or metastatic solid tumors.

1.2.2.1. Colorectal Cancer

Cytotoxic therapies are thought to have an impact on the tumor microenvironment. Oxaliplatin induces immunogenic death of colon cancer cells, and MDSCs are inhibited by 5-fluorouracil,

thereby diminishing the immunosuppressive effects on T cells (Vincent et al 2010). While FOLFOX reduces circulating MDSCs, FOLFIRI enhances the suppressive environment (Limagne et al 2016, Kanterman et al 2014).

Elevated levels of circulating or tumor-infiltrating MDSCs have been observed in CRC patients, and increased arginase 1–expressing MDSCs were reported in CRC tumor tissue compared with healthy donors (Toor et al 2016). CRC has a high frequency of tumor-infiltrating arginase 1–expressing MDSCs (see Figure 1), therefore, INCB001158 may be able to enhance the reduction of MDSCs observed with FOLFOX treatment. Thus, a FOLFOX plus INCB001158 cohort will enroll patients with advanced/metastatic MSS-CRC.

1.2.2.2. Biliary Tract Cancer

Recognition that an activated tumor microenvironment exists in biliary cancers suggests that approaches to modulating the immune system, including reversing tumor cell–induced immune suppression are relevant (Goldstein et al 2017). MDSCs freshly isolated from peripheral blood mononuclear cells are increased in patients with pancreatic or bile duct cancer as well as cholangiocarcinoma compared with those in healthy donors and correlate with clinical cancer stage (Xu et al 2016, Dunne et al 2016). Moreover, serum arginase activity in patients with gallbladder cancer is higher with advanced stages of disease.

Advanced or metastatic BTC patients will be treated with gemcitabine/cisplatin in this study, since this chemotherapy combination is the standard-of-care in the first-line setting. Moreover, since gemcitabine depletes MDSCs and Tregs and improves survival in patients and animal models (Sumida et al 2012, Shevchenko et al 2013), a gemcitabine/cisplatin plus INCB001158 cohort will enroll patients with advanced/metastatic BTC.

1.2.2.3. Ovarian Cancer

Immunotherapy is emerging as a promising approach to OC therapy (Coukos et al 2016). Tumor-infiltrating lymphocytes correlate with increased PFS and OS in advanced disease patients, whereas Treg infiltration negatively impacts survival. Furthermore, reports indicate that VEGF-induced MDSCs inhibit local immunity and contribute to poor prognosis (Horikawa et al 2017), and MDSC infiltrates isolated from OC tumor tissue mediate T-cell immune suppression *in vitro*. Therefore, immunotherapy approaches to restore antitumor immune responses might have the potential to influence prognosis in patients with epithelial OC, especially in patients with platinum-resistant disease (Mantia-Smaldone et al 2011).

Arginase activity was higher in epithelial OC patient plasma compared to healthy donors and arginase levels were decreased after chemotherapy in OC patients (Coosemans et al 2015). Arginase 1 was reported to be involved in the formation of an immunosuppressive microenvironment through exosomal arginase 1 release in body fluids including plasma or ascites from OC patients, indicating that inhibition of arginase 1 activity may be an attractive, novel anticancer strategy (Czystowska et al 2017). Despite optimal upfront surgery and the administration of front-line paclitaxel/carboplatin chemotherapy, approximately 70% of patients will relapse within the first 3 years. The prognosis and probability of response to second-line therapy and subsequent lines drops significantly, depending in great part on the progression-free interval after the last dose of the preceding line of chemotherapy. Furthermore, the category of 'resistant' patients comprises patients whose disease recurs after one or several lines of treatment.

The biological behavior of the tumor in these groups may be very variable, with differing growth rates and distribution of symptoms requiring different approaches to treatment. Treatment of patients with 'platinum-resistant' disease should be focused on quality of life and control of symptoms. Traditionally, this is a poor prognosis population with a short expected OS, usually < 12 months. Four different agents, weekly or 3-weekly paclitaxel, topotecan, PLD and gemcitabine, have been shown to have some activity in Phase 3 studies, with overall response rates not higher than 15% and a median PFS of 3 to 4 months (Luvero et al 2014). Platinum drugs continue to be used in the 'platinum-resistant' population; however, as no agent has proven to be superior to another, the selection of therapy should be based on toxicity, clinical situation of the patient, and convenience of administration. Accordingly, sequential single-agent therapy is the recommended management for this group of patients. For those patients with a later relapse (ie, over 6 months and especially over 12 months) platinum-doublet should be the treatment of choice, and studies have included carboplatin compared with the same drug combined with paclitaxel, gemcitabine, or an anthracycline. Based on the significant unmet need, encouraging preclinical data, and favorable safety profile of INCB001158, there is a robust rationale to combine the investigational drug with different chemotherapies without adding significant toxicity. Therefore, a gemcitabine/cisplatin plus INCB001158 expansion cohort (B2) and a paclitaxel plus INCB001158 expansion cohort (C3) will enroll patients with recurrent platinum-resistant OC.

1.2.2.4. Gastroesophageal Cancer

Immunotherapy approaches in patients with advanced and metastatic gastroesophageal disease are encouraging and support the investigation of immune therapies for the treatment of GC. Indeed, enhanced $CD8^+$ T-cell infiltration is observed in tumors and peritumoral interfaces in resected gastric cancers (Thompson et al 2017). MDSCs are elevated in the blood from pancreatic, gastric, and esophageal cancer patients, as well as plasma arginase 1 and Tregs; MDSCs are a prognostic factor for GC, associated with the Th2 cytokine IL-13 (Gabitass et al 2011) and the proinflammatory protein S100A8/A9.

In plasma obtained from GC patients, the levels of arginase 1 were higher than in healthy volunteers, and the levels of arginine were lower than in healthy volunteers, suggesting high arginase 1 expression in the tumor microenvironment (Figure 1). Doublet or triplet platinum/fluoropyrimidine combinations are recommended for fit patients with advanced gastric cancer. Second-line chemotherapy with a taxane (eg, docetaxel, paclitaxel), irinotecan, or ramucirumab as a single-agent or in combination with paclitaxel is recommended for patients who have an ECOG performance status of 0 to 1. In patients of adequate PS, second-line treatment is associated with proven improvements in OS and quality of life compared with best supportive care, with treatment options including irinotecan, docetaxel, or paclitaxel, if not used before. A randomized Phase 3 study directly comparing weekly paclitaxel with irinotecan has demonstrated similar efficacy for both regimens (Hironaka et al 2013). The anti–VEGFR-2 monoclonal antibody ramucirumab has shown activity in 2 randomized Phase 3 studies. As a single agent, it is associated with a survival benefit comparable to cytotoxic chemotherapy in the second-line setting, whereas ramucirumab in addition to paclitaxel is associated with a survival benefit compared with paclitaxel alone (Wilke et al 2014). Patients with metastatic esophageal cancer can be considered for different options of palliative treatment depending on the clinical situation. Treatment of advanced esophageal carcinoma is managed mostly according to the

recommendations for gastric cancer with taxanes being recommended in first-line combinations or as monotherapy in second-line settings. Therefore, based on the preclinical evidence, current standard-of-care and limited treatment options, a paclitaxel plus INCB001158 cohort will enroll patients with advanced/metastatic GC.

1.2.2.5. Endometrial Cancer

With the recognition of the limited antitumor activity of standard chemotherapy and of targeted therapy in advanced or recurrent EC patients (see Section 1.1.8), novel therapeutic approaches towards immunomodulation of the tumor microenvironment are warranted (Longoria and Eskander 2015). Indeed, the presence of intraepithelial tumor infiltrating lymphocytes (TILs) is a robust predictor of a more favorable outcome. MDSCs are detected in tumor specimens (Vanderstraeten et al 2014), and increased accumulation of MDSC in tumors is responsible for the development of chemotherapy resistance in G-CSF–producing cervical cancer (Kawano et al 2015). MSI-H EC has increased immune cell infiltration compared to MSS tumors, which might increase immunogenicity and response to immunotherapy, similarly to CRC (Pakish et al 2017). Therefore, the study will also include a paclitaxel plus INCB001158 cohort, which will enroll patients with advanced/ metastatic EC.

1.2.3. Rationale for the Dose and Schedule of INCB001158

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

As INCB001158 inhibits arginase a key enzyme in the urea cycle, urinary orotic acid elevation has been closed monitored in Study INCB 01158-101 as a marker of urea cycle inhibition. As of the 24 APR 2017 data cut-off, there were no DLTs or dose-limiting events at the 50 mg BID (n = 8) and 100 mg BID (n = 6) dose levels, and no DLTs but 2 asymptomatic dose-limiting event of elevated urinary orotic acid $\geq 5 \times$ ULN at the 150 mg BID (n = 3) dose level. Given that relatively small increases in INCB001158 doses in rats resulted in dramatic increases in urinary orotic acid levels (> 1000-fold) and toxicity (refer to the IB), it was decided to take a cautious approach and set the starting dose at least 2 dose levels below the maximum tolerated and tested dose from Study INCB 01158-101.

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

The criteria for the selection of the RP2D of INCB001158 given with each chemotherapy regimen is described in Section 4.1.1.

1.2.4. Rationale for Study Endpoints

1.2.4.1. Primary Endpoints

In Phase 1, the primary safety endpoint will assess AEs, clinical laboratory assessments, physical examination results, and 12-lead ECG results to determine the RP2D of INCB001158 in combination with each of 3 chemotherapy regimens.

In Phase 2, the primary efficacy endpoint will evaluate the ORR of INCB001158 in combination with chemotherapy by RECIST v1.1. This is a standard endpoint for assessing the antitumor activity of immunotherapies.

1.2.4.2. Secondary Endpoints

In Phase 1 and Phase 2, each antitumor activity endpoint (DCR, DOR, and PFS) will be assessed by [redacted] RECIST v1.1 [redacted]

In Phase 2, the secondary safety endpoint will assess AEs, clinical laboratory assessments, physical examination results, and 12-lead ECG results at the RP2D of INCB001158 in combination with each of 3 chemotherapy regimens.

The PK of INCB001158 given in combination with chemotherapy will be assessed using standard PK parameters.

[redacted]

1.3. Potential Risks and Benefits of the Treatment Regimen

1.3.1. Risks From INCB001158

INCB001158 is a potent and selective inhibitor of arginase 1 and arginase 2. Arginase 1 is primarily expressed in granulocytic myeloid cell granules, where it is excreted extracellularly and depletes extracellular arginine levels, and in liver hepatocytes, where it functions intracellularly as part of the urea cycle. It has been shown that INCB001158 is approximately 1000-fold more potent at inhibition of extracellular arginase 1 than intracellular arginase 1 that is engaged in the urea cycle, primarily due to poor penetration of INCB001158 across cell membranes (refer to the IB). Arginase 2 is primarily expressed in the mitochondria of many other tissues, including the gut and the kidney. The functions of arginase 2 in these tissues include regulation of systemic arginine concentration, regulation of the production of downstream products (eg, proline, polyamines), and regulation of arginine availability for 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 approximately 100-fold above baseline) has been well-tolerated in humans following intravenous administration. A ten-fold elevation in plasma arginine (to a mean concentration of 822 μM) were associated with no change in systolic or diastolic blood pressure, and a 100-fold increase in arginine was associated with mild reductions in systolic and diastolic blood pressure (~9 mmHg for each; Mehta et al 1996, Bode-Böger et al 1998).

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

There are no preclinical data available to date on the potential phototoxicity of INCB001158. Therefore, subjects enrolled in this study should be instructed by the investigator to minimize their exposure to the sun/ultraviolet light for the duration of the study and for 2 weeks after the last dose of study drug.

1.3.1.1. Potential Urea Cycle Toxicity

As detailed in the INCB001158 IB, high doses of INCB001158 that resulted in significant morbidity and mortality in mice, rats, and monkeys achieved exposures over 19-fold above the projected human efficacious exposure. In the nonclinical animal studies, the toxicity at the high doses was associated with evidence of hepatic urea cycle inhibition, including an elevation in liver arginine concentration, an increase in plasma ammonia concentration, a decrease in BUN concentration, and an increase in urinary orotic acid levels. Of particular interest, urinary orotic acid was elevated by > 1000-fold in rats at the high dose following a single dose administration prior to any signs of toxicity. Smaller elevations in urinary orotic acid were also measured in some animals at the well-tolerated mid-dose level. Elevations of urinary orotic acid have also been observed in cancer patients dosed at the highest tested dose of 150 mg BID in the first-in-human INCB 01158-101 study, although these patients were asymptomatic without signs of clinically significant urea cycle inhibition. Refer to the INCB001158 IB for the latest data and the rationale for the thresholds of OA (see Section 5.4.2) to be used in this study.

Several measures of potential toxicity related to urea cycle inhibition will be evaluated in this study (see Table 16 and Table 17). In particular, urinary orotic acid, plasma (venous) ammonia, and BUN will be measured on Day 1 and at regular intervals in the dose-escalation portion of the study (Phase 1).

Orotic acid - When the urea cycle is disrupted, the urea cycle substrate carbamoyl phosphate accumulates and is diverted into the pyrimidine synthesis pathway, producing substantial quantities of the pyrimidine precursor orotic acid. The elevated orotic acid is rapidly cleared in the urine and is used as a sensitive assay to identify defects in the urea cycle either due to inborn errors or toxic or therapeutic inhibition.

Ammonia - Urea cycle inhibition can result in large elevations in ammonia, which can lead to CNS toxicity. Inhibition of arginase, the last step in the urea cycle, does not tend to cause dramatic elevations in ammonia, but such elevations 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 affected by other factors (eg, protein consumption, fluid status/dehydration), it is not an ideal biomarker of urea cycle function. However, clear evidence of significant reduction in plasma BUN would be consistent with sustained inhibition of the hepatic urea cycle and should be avoided.

1.3.1.2. Immune-Related Adverse Events

It is not known to what extent arginine depletion is operative in normal tissues or in noncancer inflammatory states. However, 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 immuno-oncology agents in humans. Experience with other immuno-oncology agents that target endogenous immunosuppressive mechanisms has demonstrated that irAEs can affect any organ or tissue but most frequently occur in the skin (rash), gastrointestinal system (diarrhea/colitis), liver (hepatitis), lungs (pneumonitis), endocrine system (endocrinopathies due to inflammation of the pituitary, thyroid, and adrenals), and kidneys (nephritis).

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

1.3.1.3. Alterations in Hemodynamic Status

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

orthostatic hypotension will be monitored in this study as part of the standard monitoring of vital signs.

1.3.1.4. Clinical Experience

The INCB 01158-101 first-in-human study is ongoing. See Section 1.1.3.1 for early data from this study and the INCB001158 IB for more recent data. Urinary orotic acid will continue to be monitored in all clinical trials to understand the role of food and extended exposure to INCB001158 and to combinations of INCB001158 with other molecules.

1.3.2. Risks From mFOLFOX6

Oxaliplatin, a platinum-containing alkylating agent used in combination with infusional 5-fluorouracil and leucovorin, is indicated for the adjuvant treatment of Stage III colon cancer in patients who have undergone complete resection of the primary tumor and treatment of advanced CRC.

The most common adverse reactions (incidence ≥ 40%) of oxaliplatin are peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and ALP, diarrhea, emesis, fatigue, and stomatitis. Serious adverse reactions including anaphylaxis and allergic reactions, neuropathy, pulmonary toxicities, and hepatotoxicity can occur. Anaphylactic reactions to oxaliplatin may occur within minutes of administration.

In clinical trials of oxaliplatin, the most common adverse reactions in previously untreated and treated patients with advanced CRC were peripheral sensory neuropathies, fatigue, neutropenia, nausea, emesis, and diarrhea. Both 5-fluorouracil and oxaliplatin are associated with gastrointestinal and hematologic adverse reactions. When oxaliplatin is administered in combination with 5-fluorouracil, the incidence of these events is increased. Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following the administration of both oral and parenteral leucovorin.

Investigators should advise male patients to consider conservation of sperm before enrolling in the study because of the possibility of irreversible infertility after treatment with mFOLFOX6.

1.3.3. Risks From Gemcitabine/Cisplatin

Gemcitabine is a nucleoside analog with structural similarity to cytarabine, which is approved to treat breast cancer, NSCLC, OC, and pancreatic cancer either alone or in combination with other chemotherapy agents.

Cisplatin is a platinum-containing alkylating agent and is currently approved to treat ovarian germ cell cancer, invasive bladder cancer, OC, and testicular germ cell cancer either alone or in combination with other chemotherapy agents.

The combination of gemcitabine and cisplatin is indicated for use in the treatment of BTC, bladder cancer, cervical cancer, malignant mesothelioma, NSCLC, and OC.

Risks associated with use of gemcitabine include myelosuppression, which is the principal DLT. Gemcitabine can suppress bone marrow function as manifested by leukopenia, thrombocytopenia, and anemia. The most common adverse reactions as a monotherapy are

nausea; vomiting; anemia; increased ALT, AST, and ALP; neutropenia; leukopenia; proteinuria; fever; hematuria; rash; thrombocytopenia; and dyspnea.

The following cisplatin side effects are common (occurring in > 30%): nausea, vomiting, kidney toxicity (dose-related and typically reversible), neutropenia, leukopenia, and anemia. Less common side effects (occurring in 10%-29%) include the following: peripheral neuropathy; paresthesia; sensory loss; numbness and tingling; difficulty walking (some effects may be irreversible); tinnitus; anorexia; dysgeusia; increased ALT, AST, and ALP; and alopecia. Although peripheral neurotoxicity is infrequent, its incidence is increased in patients older than 65 years and in patients previously treated with cisplatin. A relationship was found between the gemcitabine dose or cisplatin frequency and the incidence of the most common hematologic (ie, anemia, neutropenia, thrombocytopenia) and nonhematologic (ie, nausea, vomiting) toxicities.

Investigators should advise male patients to consider conservation of sperm before enrolling in the study because of the possibility of irreversible infertility after treatment with gemcitabine and cisplatin.

1.3.4. Risks From Paclitaxel

Paclitaxel is a microtubule-stabilizing drug approved for the treatment of OC, breast cancer, NSCLC, pancreatic cancer, and cervical cancer and Kaposi's sarcoma and is also used in combination with other chemotherapy agents for the treatment of gastroesophageal, endometrial, prostate, and HNSCC.

Myelosuppression and neurotoxicity are common side effects of paclitaxel. Neutropenia, the most important hematologic toxicity, was dose- and schedule-dependent and was generally rapidly reversible. Peripheral neuropathy has been demonstrated to be dependent upon the dose administered, the duration of the infusion, and the schedule of administration. Nausea/vomiting, diarrhea, and mucositis were reported by 52%, 38%, and 31% of all patients, respectively. In the Phase 3 second-line OC study, infectious episodes were reported in 20% and 26% of the patients treated with a dose of 135 mg/m^2 or 175 mg/m^2 given as 3-hour infusions, respectively. Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of subjects receiving paclitaxel in clinical studies. Fatal reactions have occurred in subjects despite premedication. Weekly paclitaxel at a dose of 67 mg/m^2 was found to have a better safety profile and seemed to be as effective as the equivalently dose administration schedule of every 3 weeks in subjects with OC (Rosenberg et al 2002). Reduced toxicity (6% hematological, 4% neuropathy, 8% fatigue Grade III/IV AEs) was observed in the weekly paclitaxel GOG study (GOG 2006).

Investigators should advise male patients to consider conservation of sperm before enrolling in the study because of the possibility of irreversible infertility after treatment with paclitaxel.

1.3.5. Risks From the Combination of INCB001158 and Chemotherapy

The effects of concomitant INCB001158 with mFOLFOX6, gemcitabine/cisplatin, and paclitaxel, are being assessed in this Protocol.

As described in Sections 1.3.2, 1.3.3, and 1.3.4, the most common AEs associated with these medications are neutropenia/leukopenia, thrombocytopenia, anemia, and peripheral neuropathy. As described in Section 1.3.1, INCB001158 has been well-tolerated at the first 3 doses tested (50, 100, and 150 mg BID) in the INCB 01158-101 first-in-human study. In addition, given its mechanism of action of inhibiting arginase 1, there is not an expected overlap or interaction between these profiles. Hematology, blood chemistry, and urine parameters will be closely monitored in all study subjects. In addition, all AEs will be monitored to identify occurrences of new safety signals or potentiation of any mFOLFOX6-related, gemcitabine-related, cisplatin-related, and paclitaxel-related side effects.

1.3.6. Benefits of the Combination of INCB001158 and Chemotherapy

As described in Section 1.2.1, inhibition of arginase 1 using INCB001158 could further deepen the responses observed in multiple solid tumors with each of the 3 chemotherapy regimen used in the study by providing broader inhibition of the immunosuppressive environment driven by MDSCs, Tregs, and other immune cells and factors. It is hypothesized that this additional benefit will not come at the cost of additional toxicity (see Section 1.3.5).

2. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are presented in Table 1.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• Phase 1: To assess the safety and tolerability and determine the RP2D of INCB001158 in combination with chemotherapy.	• Safety, tolerability, DLTs, and RP2D of INCB001158 in combination with chemotherapy, as assessed by AEs, clinical laboratory tests, physical examination results, and 12-lead ECG results.
• Phase 2: To evaluate the ORR of INCB001158 in combination with chemotherapy.	• ORR, defined as the percentage of subjects having a CR or PR, as determined by investigator assessment of radiographic disease as per RECIST v1.1.
Secondary	
• Phase 2: To assess the safety, tolerability, and RP2D of INCB001158 in combination with chemotherapy.	• Safety, tolerability, and RP2D of INCB001158 in combination with chemotherapy, as assessed by AEs, clinical laboratory tests, physical examination results, and 12-lead ECG results.
• To evaluate the antitumor effect of INCB001158 in combination with chemotherapy.	• ORR, defined as the percentage of subjects having a CR or PR, as determined by investigator assessment of radiographic disease as per RECIST v1.1 (Phase 1 only). • DOR, defined as the time from earliest date of CR or PR (as determined by investigator assessment of radiographic disease assessment per RECIST v1.1) until the earliest date of disease progression or death due to any cause, if occurring sooner than disease progression. • DCR, defined as the percentage of subjects having CR, PR, or SD for at least 8 weeks, as determined by investigator assessment of radiographic disease as per RECIST v1.1. • PFS, defined as the time from date of first dose of study drug until the earliest date of disease progression (as determined by investigator assessment of radiographic disease assessment per RECIST v1.1), or death due to any cause, if occurring sooner than progression.
• To determine the PK of INCB001158 in subjects treated with INCB001158 in combination with chemotherapy.	• PK of INCB001158 will be assessed by summarizing C_{min}, C_{max}, t_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\tau}$.

Table 1: Study Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

3. SUBJECT ELIGIBILITY

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

3.1. Subject Inclusion Criteria

A subject who meets all of the following criteria may be included in the study (see Overall Study Design in Section 4.1 for the definition of the cohorts):

1. Men or women aged 18 years or older.
2. Presence of measurable disease per RECIST v1.1.

   Note: If subjects have only 1 measurable lesion per RECIST v1.1, this lesion should not have been in the field of prior irradiation unless there is documented progression of the lesion(s).
3. ECOG performance status 0 to 1.
4. Life expectancy > 12 weeks.
5. Willing 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 51 years of age).
   b. Woman of childbearing potential who has a negative serum pregnancy test at screening and before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening until 6 months after the last dose of the last component of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
   c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening until 6 months after the last dose of the last component of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
6. [redacted]
7. Willingness to undergo pretreatment and on-treatment tumor biopsies, until at least 5 evaluable paired specimens are collected in each cohort.
8. Have resolution of all toxicities and any toxic effect(s) of the most recent prior therapy to Grade 1 or less (except alopecia).
9. Adequate renal, hepatic, and hematologic functions as defined by laboratory parameters within ≤ 7 days before treatment initiation.
   a. Absolute neutrophil count ≥ 1.5×10^9/L.
   b. Platelets ≥ 100×10^9/L.

c. Hemoglobin ≥ 9 g/dL.
d. Measured or calculated CrCl (glomerular filtration rate can also be used in place of creatinine or CrCl) ≥ 50 mL/min.
   Note: Creatinine clearance should be calculated per institutional standard.
e. Total bilirubin ≤ 1.5 × ULN OR direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 × ULN.
   i. If there is no institutional normal range available for the direct bilirubin, then the direct bilirubin should be < 40% of the total bilirubin.
   ii. In no case can total bilirubin exceed 3.0 × ULN.
f. AST (SGOT) and ALT (SGPT) ≤ 2.5 × ULN.
g. INR or PT ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy, as long as PT or INR is within therapeutic range of intended use of anticoagulants.
h. Activated partial thromboplastin time ≤ 1.5 × ULN unless subject is receiving anticoagulant therapy, as long as aPTT is within therapeutic range of intended use of anticoagulants.

10. Albumin > 3.0 g/dL.
11. Phase 1 dose escalation only
    a. Subjects with histologically or cytologically confirmed advanced or metastatic solid tumors that have failed prior standard therapy (disease progression, subject refusal, or intolerance is also allowable).
       Note: There is no limit to the number of prior treatment regimens.
    b. Locally advanced disease must not be amenable to resection with curative intent.
12. Phase 2 Expansion Cohort A1: MSS-CRC subjects only
    a. Subjects with histologically or cytologically confirmed advanced or metastatic adenocarcinoma of the colon or rectum.
       Note: Should have documented MSS status, or consent to local institutional MSI testing during the screening period.
       Note: Must have received at least 1, but not more than 2, prior chemotherapy regimen for locally advanced/metastatic CRC, including fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy with or without anti-VEGF therapy (if no contraindication).
       Note: Subjects who completed a fluoropyrimidine-, irinotecan-, or oxaliplatin-based chemotherapy regimen as adjuvant, neoadjuvant, or part of a course of chemoradiation therapy and progressed ≥ 6 months after completing therapy will be eligible. If progression occurred < 6 months after completing therapy, then the subject will not be eligible.
13. Phase 2 Expansion Cohort B1: BTC subjects only
    a. Subjects with histologically or cytologically confirmed nonresectable advanced or metastatic biliary tract carcinoma (intra- or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma).
       Note: Should not have received prior systemic chemotherapy for metastatic or inoperable locally advanced BTC (not including adjuvant therapy completed at least 6 months prior to enrollment).

14. Phase 2 Expansion Cohort B2: OC subjects only

    a. Subjects with histologically confirmed recurrent epithelial ovarian, peritoneal, or fallopian tube carcinoma and carcinosarcomas (Sertoli-Leydig or germ cell cancers are excluded) that have progressed within 6 months of prior cytotoxic chemotherapy.
    Note: Should have received at least 1 and no more than 4 prior therapies, and failed at least 1 standard line of chemotherapy.
    Note: Adjuvant regimens given within 6 months of screening would be counted as first-line therapy.

15. Phase 2 Expansion Cohort C1: GC subjects only

    a. Subjects with histologically or cytologically confirmed advanced or metastatic adenocarcinoma of the stomach, esophagus, or GEJ.
    Note: Should have received only 1 prior chemotherapy regimen for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy). Adjuvant regimens given within 6 months of screening would be counted as first-line therapy.

16. Phase 2 Expansion Cohort C2: EC subjects only

    a. Subjects with histologically or cytologically confirmed advanced or metastatic endometrial carcinoma.
    Note: Should have documented MSI status (eg, MSI-H, MSI-low, MSS), or consent to local institutional MSI testing during the screening period.
    Note: Should have received at least 1, but not more than 2, prior chemotherapy regimens for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy). Adjuvant regimens given within 6 months of screening would be counted as first-line therapy.
    Note: May have received prior hormonal and/or biological therapy in addition to prior systemic chemotherapy, which will not count as prior therapy.

17. Phase 2 Expansion Cohort C3: OC subjects only

    a. Subjects with histologically confirmed recurrent epithelial ovarian, peritoneal or fallopian tube carcinoma and carcinosarcomas that have progressed within 6 months of prior cytotoxic chemotherapy (Sertoli-Leydig or germ cell cancers are excluded).
    Note: Should have received no more than 5 prior therapies and failed at least 1 standard (platinum-containing) chemotherapy regimen and be considered platinum-resistant.
    Note: Adjuvant regimens given within 6 months of screening would be counted as first-line therapy.

3.2. Subject Exclusion Criteria

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

1. Participation in any other study in which receipt of an investigational study drug or device occurred within 28 days or 5 half-lives (whichever is longer) before first dose. For investigational agents with long half-lives (eg, 5 days), enrollment before the fifth half-life requires medical monitor approval.
2. Has received a prior monoclonal antibody within 4 weeks or 5 half-lives (whichever is shorter) before administration of study drug.
   a. Exception: Washout of immune checkpoint inhibitor therapy is NOT required.
   b. Exception: Denosumab may be used.
3. Has had prior chemotherapy or targeted small molecule therapy within 2 weeks before administration of study treatment.
4. Has received prior approved radiotherapy within 14 days of study therapy (exception for radiation to CNS, which requires ≥ 28-day washout as described below).

   Note: Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of RT) to non-CNS disease.
5. Subjects must not have received therapy with an arginase inhibitor.

   Note: Prior immunotherapy treatment with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti–CTLA-4, anti-CD137, or any other antibody or drug specifically targeting immune checkpoint pathways is allowed.
6. Has had major surgery within 4 weeks before enrollment (C1D1).
7. Has had known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 2 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy, or cancers from which the subject has been disease-free for > 1 year, after treatment with curative intent.
8. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (exceeding 10 mg daily of prednisone equivalent in dose) or any other form of immunosuppressive therapy within 7 days before the first dose of study treatment.
9. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).

   Note: Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
10. Has a known history of HIV infection. HIV testing is not required unless mandated by the local health authority.

11. Has a known history of or is positive for hepatitis B (HBsAg reactive) or hepatitis C.

    Note: Testing must be performed to determine eligibility.

    a. HBV DNA must be undetectable and HBsAg negative at screening visit.
    b. Hepatitis C antibody testing is allowed for screening purposes in countries where HCV RNA is not part of standard-of-care treatment. In these cases, HCV antibody–positive patients will be excluded.
    c. Subjects who have had definitive treatment for HCV are permitted if HCV RNA is undetectable at screening visit.

12. Has known active CNS metastases and/or carcinomatous meningitis.

    Note: Subjects with previously treated brain metastases may participate provided that they are stable (without evidence of progression by imaging for at least 28 days before the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or cerebral edema, and have not required steroids for at least 14 days before the first dose of study drug.

    Note: Subjects with evidence of cerebral edema or those with < 28 days since RT to the CNS will be excluded from study.

13. Has not recovered to ≤ Grade 1 from toxic effects of previous therapy and/or complications from previous surgical intervention before starting study therapy.

    Note: Subjects with stable chronic AEs (≤ Grade 2) not expected to resolve (eg, alopecia) are exceptions and may enroll.

    Note: Subjects with a history of peripheral neuropathy ≥ Grade 2 will be excluded.

14. Has a known or suspected defect in the function of the urea cycle, including a known deficiency of carbamoyl phosphate synthetase I, ornithine transcarbamylase, argininosuccinate synthetase, argininosuccinate lyase, N-acetyl glutamate synthetase, or arginase.

15. Has had a significant cardiac event within 6 months before Cycle 1 Day 1, including myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, or pulmonary embolism. Medically controlled arrhythmia is permitted.

16. Has a history or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 ms is excluded (corrected by Fridericia formula). In the event that a single QTc is > 480 ms, the screening ECG may be repeated in triplicate, and the subject may enroll if the average QTc is < 480 ms.

17. Concomitant therapy with valproic acid/valproate-containing therapies.

18. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live-attenuated vaccines and are not allowed.

19. Current use of any prohibited medication as described in Section 5.6.3.
20. Evidence of interstitial lung disease or active, noninfectious pneumonitis.
21. Inability to swallow food or any condition of the upper gastrointestinal tract that precludes administration of oral medications.
22. Active infection requiring systemic therapy.
23. Has known hypersensitivity to any of the active substances or any of their excipients, including mannitol.
24. Women who are pregnant or breastfeeding.
25. Subjects with bleeding associated with tumors in proximity to major blood vessels are excluded except with medical monitor approval.
26. Has a history of a gastrointestinal condition (eg, inflammatory bowel disease, Crohn's disease, ulcerative colitis) that may affect drug absorption.
27. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

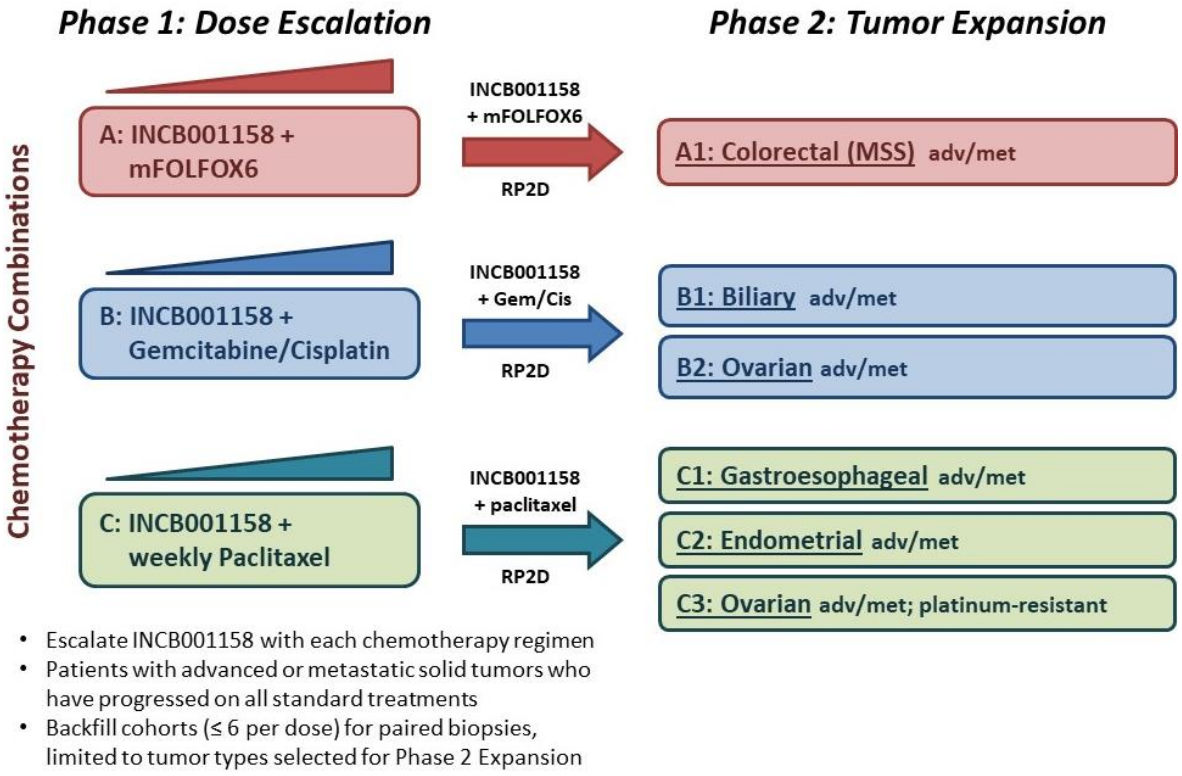
This is an open-label, nonrandomized, Phase 1/2 study to evaluate the safety, tolerability, and antitumor activity of INCB001158 in combination with 3 different chemotherapy regimens (Figure 2). Phase 1 will consist of dose-escalation using a BOIN design (Liu and Yuan 2015) and will determine the RP2D of INCB001158 when given in combination with each chemotherapy regimen; efficacy will also be explored. Subjects with advanced or metastatic solid tumors for whom treatment with one of the chemotherapy regimens is appropriate will be enrolled in Phase 1.

Phase 2 will evaluate ORRs using a Simon 2-stage design to determine whether the combinations have sufficient antitumor activity to warrant further testing in subsequent clinical studies and will further evaluate the safety and tolerability of the RP2D of INCB001158 when given in combination with chemotherapy. Subjects with advanced or metastatic CRC, BTC, OC, GC, and EC will be enrolled in the Phase 2 expansion cohorts.

See Section 4.1.1 for full details of the Phase 1 dose escalation, Section 4.1.2, for full details of Phase 2 tumor expansion, and Section 5.2 for full study drug administration information.

The definition of DLTs is provided in Section 5.4.2.

Figure 2: Study Design



4.1.1. Phase 1: Dose Escalation of INCB001158 + Chemotherapy

In Phase 1, a BOIN design will be used to determine the RP2D of the combination of INCB001158 and chemotherapy in 21-day (for gemcitabine/cisplatin) or 28-day (for mFOLFOX6 or paclitaxel) treatment cycles in subjects with advanced or metastatic solid tumors. The RP2D will then be further assessed in tumor expansion cohorts in Phase 2.

Subjects with advanced or metastatic solid tumors will be assigned to 1 of the treatment groups summarized in Table 2 based on the chemotherapy regimen most appropriate for the subject's tumor type.

Table 2: Treatment Groups for Subjects Enrolled in Phase 1 Dose Escalation

Treatment Group A	**INCB001158**	**mFOLFOX6**
	25-150 mg PO BID continuous daily dosing	Oxaliplatin 85 mg/m^2 IV on Day 1 and Day 15 of a 28-day cycle Leucovorin 400 mg/m^2 IV on Day 1 and Day 15 of a 28-day cycle 5-Fluorouracil 400 mg/m^2 IV bolus on Day 1 and Day 15, then 1200 mg/m^2 per day IV infusion over 46 hours for a total dose of 2400 mg/m^2 on Day 1 and Day 15 of a 28-day cycle
Treatment Group B	**INCB001158**	**Gemcitabine and Cisplatin**
	25-150 mg PO BID continuous daily dosing	Gemcitabine 1000 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle Cisplatin 30 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle
Treatment Group C	**INCB001158**	**Paclitaxel**
	25-150 mg PO BID continuous daily dosing	Paclitaxel 80 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle

BID = twice daily; IV = intravenous; PO = orally.

Dose escalation will begin with starting doses of INCB001158 at least 2 dose levels below the maximum tolerated and tested dose from the INCB 01158-101 study (likely to be 50 mg BID or 75 mg BID) – see Table 3, Column A and B, respectively.

Table 3: INCB001158 Dose Cohorts

	INCB001158 Dose Levels for Phase 1	
INCB001158 Dose Cohort	**A. Starting Dose of 50 mg BID**	**B. Starting Dose of 75 mg BID**
-1	25 mg BID	50 mg BID
1 (starting dose)	**50 mg BID[a]**	**75 mg BID[b]**
2	75 mg BID	100 mg BID
3	100 mg BID	150 mg BID
4	150 mg BID	N/A

BID = twice daily.
[a] If INCB001158 50 mg BID is not tolerated within a treatment group, INCB001158 25 mg BID may be evaluated.
[b] If INCB001158 75 mg BID is not tolerated within a treatment group, INCB001158 50 mg BID may be evaluated.

If the starting dose is not 1 of those 2 dose levels, dose escalation will follow the same pattern, and the exact dose escalation table will be provided to sites. The INCB001158 dose will be escalated using an open-label BOIN design in each chemotherapy regimen, and a PAD or the MTD will be determined, or the maximum dose of INCB001158 (150 mg BID) will be reached. A PAD of INCB001158 is defined as a dose that achieves a trough (C_{min}) plasma concentration of INCB001158 at steady state of ≥ 1 µM that is equivalent to the IC_{90} for arginase 1. This definition may be modified based on emerging data from the INCB 01158-101 first-in-human study, upon agreement between the medical monitor and the study investigators. The MTD is the maximum tolerated or tested dose of INCB001158, such that fewer than 33% of the subjects

receiving the combination experience a DLT during the first 28 days on study drug. After the dose escalation is completed, one of the INCB001158 dose levels that is pharmacologically active and tolerable in combination with each chemotherapy regimen (ie, MTD or lower) will be the RP2D.

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

Dose escalation and de-escalation in Phase 1 will follow the BOIN design algorithm. Given the target DLT rate of 33% for the INCB001158 in combination with chemotherapy, the dose escalation and de-escalation rules are shown in Table 4. The BOIN design also includes an elimination rule. When ≥ 3 subjects have been treated, if the probability that the estimated toxicity rate that is above the target DLT rate is > 95% at a certain dose level, then this dose level and higher dose levels are assumed to be too toxic and will be eliminated. If the lowest dose level is eliminated, then the whole dose escalation will be terminated. Table 4 (in the bottom row) provides the elimination rules. Based on this algorithm, a minimum of 3 evaluable subjects and a maximum of 9 evaluable subjects will be enrolled at each tested dose level. The dose escalation will continue, based on the rules in Table 4, until at least 1 of the following occurs:

- Enrollment of additional subjects in a dose cohort that already has 9 evaluable subjects, or
- Dose escalation to a dose level that has already been eliminated, or
- Dose escalation above the maximum allowable dose level identified in the INCB 01158-101 study (see Section 1.2.3).

At that point, the dose escalation will be stopped.

Table 4: Dose Escalation, De-Escalation, and Elimination Boundaries for Target DLT Rate of 33% in Phase 1

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

DLT = dose-limiting toxicity.

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

When applying the BOIN design, a maximum of 9 evaluable subjects will be used at each dose level for initially identifying the MTD; however, the MTD of INCB001158 for one of the chemotherapy combinations may be a dose level below the other MTDs. After the PADs or MTDs are selected for each of the 3 combinations, the cohort may be expanded to 12 (and then

to 15) in one of the chemotherapy combinations, and an MTD will be redetermined if all the following conditions are satisfied.

- If and only if a single one of the chemotherapy combinations has a lower MTD than the others.
- The Incyte medical monitor and the investigators review the entirety of the safety data and agree that the dose with the lower MTD needs to be re-challenged.
- The de-escalation and elimination boundaries are not crossed during the dose rechallenge and dose levels are retested. (Neither the de-escalation nor the elimination boundaries are touched.)

For expanding the cohorts, the decisions rules are presented in Table 5.

Table 5: Dose Escalation, De-Escalation, and Elimination Boundaries for Target DLT Rate of 33% for Cohort Expansion in Phase 1

	Number of Subjects Treated at the Current Dose					
Action	**10**	**11**	**12**	**13**	**14**	**15**
Escalate if # of DLTs ≤	2	2	3	3	3	3
De-escalate if # of DLTs ≥	4	5	5	6	6	6
Elimination if # of DLTs ≥	6	7	7	8	8	8

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

4.1.2. Phase 2: Tumor Expansion Cohorts of INCB001158 + Chemotherapy

To determine whether the combinations result in adequate ORRs to warrant further testing in subsequent clinical studies, a Simon 2-stage design will be used for each tumor expansion cohort to evaluate the ORR of the RP2D of INCB001158 determined in Phase 1 in combination with chemotherapy and further evaluate the safety and tolerability of the combination. If, at the time of completion of enrollment in Stage 1, it is not known whether the target ORR to proceed to Stage 2 will be met, then enrollment will be paused until and unless the ORR to proceed has been met.

Enrollment in a specific expansion cohort will begin when the RP2D of INCB001158 for the corresponding treatment group in Phase 1 has been determined.

The expansion cohorts will be limited to the following advanced/metastatic or recurrent tumor types:

- Cohort A1: MSS-CRC (INCB001158 + mFOLFOX6)
- Cohort B1: BTC (INCB001158 + gemcitabine/cisplatin)
- Cohort B2: OC (INCB001158 + gemcitabine/cisplatin)
- Cohort C1: GC (INCB001158 + paclitaxel)
- Cohort C2: EC (INCB001158 + paclitaxel)
- Cohort C3: OC (INCB001158 + paclitaxel)

Subjects will be assigned to the expansion cohorts summarized in Table 6.

Table 6: Expansion Cohorts for Subjects Enrolled in Phase 2 Tumor Expansion

Expansion Cohort A1	**INCB001158**	**mFOLFOX6**
	PO BID continuous daily dosing	Oxaliplatin 85 mg/m^2 IV on Day 1 and Day 15 of a 28-day cycle Leucovorin 400 mg/m^2 IV on Day 1 and Day 15 of a 28-day cycle 5-Fluorouracil 400 mg/m^2 IV bolus on Day 1 and Day 15, then 1200 mg/m^2 per day IV infusion over 46 hours for a total dose of 2400 mg/m^2 on Day 1 and Day 15 of a 28-day cycle
Expansion Cohort B1	**INCB001158**	**Gemcitabine and Cisplatin**
	PO BID continuous daily dosing	Gemcitabine 1000 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle Cisplatin 25 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle
Expansion Cohort B2	**INCB001158**	**Gemcitabine and Cisplatin**
	PO BID continuous daily dosing	Gemcitabine 750 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle Cisplatin 30 mg/m^2 IV infusion on Days 1 and 8 of a 21-day cycle
Expansion Cohorts C1, C2, and C3	**INCB001158**	**Paclitaxel**
	PO BID continuous daily dosing	Paclitaxel 80 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle

BID = twice daily; IV = intravenous; PO = orally.

Continuous evaluation of toxicity events will be performed in the expansion cohorts. If the cumulative incidence of ≥ Grade 3 INCB001158-related AEs or ≥ Grade 3 chemotherapy-related AEs is > 40% after 10 subjects are enrolled in a specific expansion cohort within Phase 2, then further enrollment in that cohort will be interrupted until the sponsor and investigators determine the appropriate course of action. If an expansion cohort is discontinued due to toxicity, a new cohort may be initiated at a previously tested lower dose level.

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

In each cohort, a Simon 2-stage design will be used to assess the antitumor activity of the INCB001158 + chemotherapy combination (see Table 7), to determine whether the combination results in sufficient antitumor activity to warrant further testing in subsequent clinical studies.

Table 7: Phase 2: Simon 2-Stage Design

Cohort (Tumor Type)	Background ORR	Target ORR	Alpha	Power	N for Stage 1	ORR to Proceed	N for Stage 2	ORR for Positive Cohort
A1 (MSS-CRC)	10%	30%	0.1	80	7	≥ 1/7	11	≥ 4/18
B1 (BTC)	20%	40%	0.1	80	12	≥ 3/12	13	≥ 8/25
B2 (OC)	15%	35%	0.1	80	9	≥ 2/9	14	≥ 6/23
C1 (GC)	15%	35%	0.1	80	9	≥ 2/9	14	≥ 6/23
C2 (EC)	15%	35%	0.1	80	9	≥ 2/9	14	≥ 6/23
C3 (OC)	15%	35%	0.1	80	9	≥ 2/9	14	≥ 6/23

Note: See Sections 1.1 and 1.2 for background and target ORRs rationale for each cohort.

At certain prespecified study sites, mandatory paired predose and on-treatment tumor biopsies will be collected from subjects (unless it is not considered to be safe or otherwise is not feasible), until approximately 5 evaluable paired specimens are collected in each treatment cohort. Collection of paired biopsies is optional in subjects subsequently enrolled at those sites and for all subjects enrolled at other sites.

If either cohort completes enrollment, based on the Simon 2-stage design, before sufficient evaluable paired biopsies have been collected, then enrollment may continue at the prespecified, investigative sites until approximately 5 evaluable paired specimens have been collected in each cohort.

[redacted]

4.2. Measures Taken to Avoid Bias

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

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Up to a total of 222 subjects (if starting dose level is 75 mg in Phase 1) or up to a total of 249 (if starting dose level is 50 mg in Phase 1) are planned for enrollment. This may vary due to the number of subjects required to determine the target dose.

- Phase 1 dose escalation – Up to 87 (if starting dose level is 75 mg in Phase 1) or up to 114 (if starting dose level is 50 mg in Phase 1) evaluable subjects.
- Phase 2 tumor expansion (Simon 2-stage) – Approximately 55 to 135 evaluable subjects

It is planned to have 4 to 5 sites during Phase 1 dose escalation and approximately 11 to 16 additional sites during Phase 2 tumor expansion.

4.3.2. Replacement of Subjects

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

In the tumor expansion in Phase 2, enrollment will continue in each expansion cohort until there are sufficient subjects who are evaluable for each stage of the Simon 2-Stage design (see Section 4.1.2 for definition). [redacted]

4.4. Duration of Treatment and Subject Participation

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

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. The end of the study will occur when all subjects have completed applicable follow-up assessments or when the sponsor terminates the study.

If there have been ≤ 5 subjects on study for more than 6 months, then 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 subject population. In addition, the investigator will be expected to monitor for and report any SAEs, AESIs, and pregnancies per the study assessments in Section 8. The remaining subjects are considered to be on study until a discontinuation criterion is met and written notification is provided to the sponsor.

4.6. Study Termination

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

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

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Each subject will be identified in the study by a subject ID number, which is a combination of the site ID and subject number. Site staff should contact the IRT to obtain the subject ID number during screening. This subject ID number will be maintained throughout the study and will not be reassigned. Subjects who fail screening and are repeating the screening process due to a change in eligibility status will be assigned a new subject ID number. For subjects who signed an ICF but are not treated, refer to the eCRF Completion Guidelines for instructions on which eCRFs to complete.

Site staff will contact the IRT to obtain the initial study drug assignment. The investigator or designee will select the assigned study drug from their stock that corresponds to the number provided by the IRT, record the unique identifiers in the eCRF, and dispense the study drug to the subject. All subsequent dispensing of study drug should follow this process. Full details will be provided in the IRT manual.

If a subject is mistakenly given a bottle of study drug that is not the bottle assigned by the IRT, then the IRT help desk must be notified immediately. The reason for the misallocation of the study drug must be documented by the study site.

5.1.2. Randomization and Blinding

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

5.2. 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 4 investigational study treatments in this study – INCB001158, mFOLFOX6, gemcitabine/cisplatin, and paclitaxel. INCB001158 is also referred to as the study drug in this Protocol.

5.2.1. INCB001158

5.2.1.1. Description and Administration

INCB001158 will be administered PO BID using a tablet (25 mg or 100 mg per tablet) formulation. Doses will be taken in the morning and evening, approximately 12 hours apart. INCB001158 will be administered on Days 1 through 28 of each 28-day cycle (mFOLFOX6 and paclitaxel treatment groups) or on Days 1 through 21 of each 21-day cycle (gemcitabine/cisplatin treatment group) and should be taken PO using the number of tablets directed in the Pharmacy Manual. The starting dose will depend on which phase and cohort of the study that the subject is in. In Phase 1, the starting dose will be based on which dose level cohort that the subject is in; in Phase 2, the starting dose will be the RP2D identified in Phase 1. INCB001158 dose regimens will not be adjusted for body weight or surface area.

INCB001158 will be administered beginning on Cycle 1 Day 1 and continuously thereafter. On days when INCB001158 is administered in the clinic, INCB001158 should be taken before beginning the infusion of the applicable chemotherapy regimen (mFOLFOX6, gemcitabine/cisplatin, or paclitaxel).

INCB001158 will be given daily for as long as disease progression has not occurred and criteria for treatment discontinuation have not been met.

5.2.1.2. Supply, Packaging, and Labeling

INCB001158 will be provided to sites by Incyte.

Study drug will be supplied as INCB001158 25 mg or 100 mg tablets packaged in bottles. No preparation is required. All tablet excipients comply with the requirements of the applicable compendial monographs (Ph Eur, USP/NF; refer to the IB).

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

5.2.1.3. Storage

Bottles of INCB001158 tablets should be stored at room temperature, 15°C to 30°C (59°F to 86°F). Subjects will be requested to store the study drug at the recommended storage conditions noted on the label and out of the reach of children or other cohabitants.

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

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

- To store the study drug at room temperature.
- To only remove from the study drug bottle the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- Not to split or crush tablets.
- To make every effort to take doses on schedule.

- To report any missed doses.
- To take study drug at approximately the same times each day without respect to food (except on Protocol-defined clinic days, when the subject should fast for at least 8 hours before taking study drug) and with a full glass of water. The second dose on any given day should be taken approximately 12 hours after the first dose.
- Subjects who vomit their INCB001158 dose should be instructed NOT to make up that dose and to report the frequency of vomiting occurrences associated with study drug administration to the site. Subjects who report ≥ 3 incidences of vomiting associated with study drug administration will have a blood sample drawn for an unscheduled PK analysis.
- To bring all used and unused study drug bottles to the site at each visit.
- Missed doses of INCB001158 should be skipped. If a subject forgets to take a dose of study drug and he/she is outside of the allotted window period (± 6 h), he/she should be instructed to skip that dose and NOT take extra study drug at their next administration.

On Protocol-defined clinic days (see Table 11, Table 12, Table 13, and Table 14; see Table 15 for all subjects as of Protocol Amendment 4) subjects should be instructed NOT to take their morning dose of INCB001158 at home. The morning dose must be administered at the clinical site after all predose procedures have been performed. The time of dose administration will be recorded in the clinic. The evening doses will be self-administered by the subject after all postdose activities have been completed.

5.2.2. mFOLFOX6

5.2.2.1. Description and Administration

Subjects will receive oxaliplatin 85 mg/m^2 IV given concurrently with leucovorin 400 mg/m^2 IV over 2 hours ± 15 minutes (or equivalent dose and schedule based on institutional practice), followed by a 5-fluorouracil 400 mg/m^2 IV bolus (administration time per institutional practice), then a 5-fluorouracil 1200 mg/m^2 per day IV continuous infusion over 46 hours for a total dose of 2400 mg/m^2. These 3 agents will be administered on Day 1 and Day 15 of each 28-day cycle after administration of INCB001158. Investigators may reduce or discontinue oxaliplatin for peripheral neuropathy; if discontinued, investigators have the option to discontinue 5-fluorouracil and leucovorin. Subjects must meet minimum criteria for the start of each chemotherapy cycle as outlined in Appendix C, Section C.1.

The Pharmacy Manual provides additional information and instructions for preparation and infusion of 5-fluorouracil, leucovorin, and oxaliplatin.

Subjects may receive prophylactic G-CSF support with filgrastim. Granulocyte-colony stimulating factor should not be given in the first cycle. If chemotherapy is held for toxicity, then prophylactic G-CSF support should also be held. Additionally, if chemotherapy is held because of neutropenia, then G-CSF may be administered to treat neutropenia per institutional guidelines. Granulocyte-colony stimulating factor support can be held for ANC levels ≥ 4.0 × 10^9/L at the investigator's discretion.

5.2.2.2. Supply, Packaging, Labeling, and Storage

In countries where 5-fluorouracil, leucovorin, oxaliplatin, filgrastim, or their generic equivalents are commercially available, investigators are responsible for ensuring that subjects receive commercially available supplies of these therapies for the entire duration of study participation. Incyte may provide certain reference therapies where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to these therapies.

5.2.3. Gemcitabine/Cisplatin

5.2.3.1. Description and Administration

For Phase 1 dose escalation, subjects with advanced or metastatic disease will receive gemcitabine 1000 mg/m^2 IV over 30 minutes (± 5 min) and cisplatin 30 mg/m^2 IV over 30 minutes (± 5 min) on Days 1 and 8 of each 21-day cycle.

For Phase 2 tumor expansion, subjects will receive the gemcitabine/cisplatin regimen that is the standard dose and schedule used for the corresponding tumor type patients:

- In Cohort B1 (BTC), subjects will receive gemcitabine 1000 mg/m^2 IV over 30 minutes (± 5 min) and cisplatin 25 mg/m^2 IV over 30 minutes (± 5 min) on Days 1 and 8 of each 21-day cycle.
- In Cohort B2 (OC), subjects will receive gemcitabine 750 mg/m^2 IV over 30 minutes (± 5 min) and cisplatin 30 mg/m^2 IV over 30 minutes (± 5 min) on Days 1 and 8 of each 21-day cycle.

Subjects must meet minimum criteria for the start of each chemotherapy cycle as outlined in Appendix D, Section D.1.

The Pharmacy Manual provides additional information and instructions for preparation and infusion of gemcitabine and cisplatin.

Subjects may receive prophylactic G-CSF support with filgrastim. Granulocyte-colony stimulating factor should not be given in the first cycle. If chemotherapy is held for toxicity, then prophylactic G-CSF support should also be held. Additionally, if chemotherapy is held because of neutropenia, then G-CSF may be administered to treat neutropenia per institutional guidelines. Granulocyte-colony stimulating factor support can be held for ANC levels $\geq 4.0 \times 10^9$/L at the investigator's discretion.

5.2.3.2. Supply, Packaging, Labeling, and Storage

In countries where gemcitabine and cisplatin (or its generic equivalents) are commercially available, investigators are responsible for ensuring that subjects receive commercially available supplies of these therapies for the entire duration of study participation. Incyte may provide certain reference therapies where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to these therapies.

5.2.4. Paclitaxel

5.2.4.1. Description and Administration

Subjects will receive weekly paclitaxel 80 mg/m^2 IV infusion over 1 hour (± 10 min) on Days 1, 8, and 15 of each 28-day cycle.

Subjects must meet minimum criteria for start of each chemotherapy cycle as outlined in Appendix E, Section E.1.

The Pharmacy Manual provides additional information and instructions for preparation and infusion of paclitaxel.

Subjects must receive premedication; for example, see Table 8. Alternative institutional premedications are allowed.

Table 8: Recommended Premedication Schedule

Drug	Dose	Route	Administration
Dexamethasone	8 mg	IV	30-60 minutes before paclitaxel infusion
Chlorphenamine	10 mg	IV	30-60 minutes before paclitaxel infusion over at least 1 minute
Ranitidine	50 mg	IV	30-60 minutes before paclitaxel infusion over at least 2 minute

It may not be necessary to stop treatment for minor hypersensitivity (eg, reactions, flushing, localized rash). Infusions must be stopped for major reactions (eg, hypotension, dyspnea, angioedema, or generalized urticarial).

Subjects may receive prophylactic G-CSF support with filgrastim. Granulocyte-colony stimulating factor should not be given in the first cycle. If chemotherapy is held for toxicity, then prophylactic G-CSF support should also be held. Additionally, if chemotherapy is held because of neutropenia, then G-CSF may be administered to treat neutropenia per institutional guidelines. Granulocyte-colony stimulating factor support can be held for ANC levels $\geq 4.0 \times 10^9$/L at the investigator's discretion.

5.2.4.2. Supply, Packaging, Labeling, and Storage

In countries where paclitaxel or generic equivalent is commercially available, investigators are responsible for ensuring that subjects receive commercially available supplies of these therapies for the entire duration of study participation. Incyte may provide certain reference therapies where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to these therapies.

5.3. Treatment Compliance

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

5-Fluorouracil, leucovorin, oxaliplatin, gemcitabine, cisplatin, and paclitaxel are administered intravenously by site personnel. Receipt of infusions will be documented by the site staff and monitored by the sponsor or designee.

5.4. Treatment Interruptions and Adjustments

5.4.1. Dose Modifications

Selections and modifications to the study drug regimen are planned for the Phase 1 dose-escalation cohorts. Dose interruptions and modifications also may occur for individual study subjects. The identification of DLTs will define the doses used in planned dose cohorts (see Section 4.1.1). Dose modifications in the form of reductions, interruption, or discontinuation for any of the study treatments (INCB001158 or chemotherapy regimen) may also be needed for individual subjects in the event of a DLT or AE (related or unrelated to study treatment). Intrasubject dose escalation for any study drug is not permitted.

5.4.1.1. INCB001158

For subjects in Phase 1, dose reductions of INCB001158 will be permitted during the first 28 days only if a subject experiences a DLT or a toxicity that may herald a DLT. If a subject experiences a DLT, treatment continuation at a lower dose of INCB001158 will be permitted as long as the toxicity has returned to ≤ Grade 1 or baseline within 28 days. When INCB001158 is held or discontinued, chemotherapy may be continued, at the investigator's discretion. Upon recovery, subjects may restart at 1 INCB001158 dose level lower. Subjects who do not recover within 28 days will not be eligible for resumption of study treatment without approval from the medical monitor. See also Table 10.

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

Dose-limiting toxicity will be defined as the occurrence of any of the toxicities in Table 9 occurring up to and including Day 28, except those with a clear alternative explanation (eg, disease progression) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination. All DLTs will be assessed by the investigator using CTCAE v4.03 criteria. For INCB001158 at the dose level assigned, subjects who receive at least 32 of 42 doses for 21-day cycle regimens and at least 42 of 56 doses for 28-day cycle regimens (both representing ≥ 75% of the dose planned), or subjects who have a DLT will be considered evaluable for determining tolerability of the dose. Subjects who do not meet these criteria may be replaced to obtain sufficient evaluable subjects to be able to assess that dose level using the BOIN design, as outlined in Table 4.

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

Individual subject dose reductions for INCB001158 may be made based on events observed at any time during treatment; however, for the purposes of dose cohort escalation/de-escalation,

expanding a dose cohort, and determining the MTD of INCB001158, decisions will be made based on events that are observed from the first day of study drug administration through and including Day 28. A lower MTD may subsequently be determined based on relevant toxicities that become evident after Day 28.

Table 9: Definition of Dose-Limiting Toxicity

Toxicity
Nonhematologic
• Any ≥ Grade 3 nonhematologic toxicity EXCEPT: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. – Changes in cholesterol and triglycerides. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. – Asymptomatic changes in lipid profiles. – Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions).
Hematologic
• Grade 3 thrombocytopenia with bleeding. • Grade 4 thrombocytopenia. • Any grade febrile neutropenia (ANC < 1.0×10^9/L and fever > 101°F/38.5°C). • Grade 4 neutropenia that does not recover to ≤ Grade 2 in ≤ 7 days after interrupting study drug. • Grade 4 anemia not explained by underlying disease or some other concomitant disorder.
Immune-related toxicity
• ≥ Grade 2 ocular irAEs will be considered a DLT. • Grade 3 irAEs that do not improve to baseline or at least Grade 1 in < 5 days with appropriate care or with corticosteroid therapy will be considered a DLT. *Exception:* Grade 3 rash in the absence of desquamation, with no mucosal involvement, that does not require systemic steroids, and that resolves to Grade 1 within 14 days. • Grade 4 irAEs will be considered a DLT regardless of duration. • ≥ Grade 2 pneumonitis.
General
• The inability to receive ≥ 75% of INCB001158 doses during the DLT-evaluation period (28 days) due to a drug-related AE will be considered a DLT. • Any other AE that is felt to be treatment-limiting in the medical opinions of the principal investigator and the medical monitor may be considered a DLT.

AE = adverse event; ANC = absolute neutrophil count; DLT = dose-limiting toxicity; irAE = immune-related adverse event.
Note: Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination will not be considered a dose-limiting toxicity.

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

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

5.4.4. Follow-Up of Dose-Limiting Toxicities

Any DLT should be followed until it resolves to baseline or appears to have stabilized for a minimum of 4 weeks, unless the subject discontinues study treatment, in which case, the subject will be followed for 90 days after last dose of study treatment (see Section 8). During follow-up, subjects should be seen as often as medically indicated to assure safety.

5.4.5. Procedures for Cohort Review and Dose Escalation

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

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

As described in Section 1.3.1, INCB001158 has the potential to cause toxicity related to the inhibition of arginase 1 in the hepatic urea cycle.

Table 10 provides guidance for INCB001158 dose modifications and subject management if there is evidence of urea cycle inhibition.

Dose modification and toxicity management for irAEs associated with INCB001158 should be managed as follows.

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

Table 10 summarizes the AE dose modification actions for INCB001158. Of note, when indicated by Table 10 to mitigate irAEs, the dose of INCB001158 must be reduced using the dosing levels outlined in Table 4. Once reduced, re-escalation of INCB001158 is not permitted.

Table 10: Dose Modification and Toxicity Management Guidelines for Adverse Events Related to INCB001158

Adverse Event	Toxicity Grade or Conditions (CTCAEv4.03)	Action Taken	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Evidence of urea cycle inhibition	• Fasting urinary orotic acid > 2 × and ≤ 10 × ULN • Any urinary orotic acid > 2 × and ≤ 40 × ULN	• Continue.	• None.	• Retest fasting urinary orotic acid 1 week later.
	• Ammonia 2 × ULN and 2 × baseline (repeated measurements or with symptoms) • Fasting urinary orotic acid > 10 × ULN • Any urinary orotic acid > 40 × ULN • BUN < 50% LLN	• Withhold. • Consider restarting (at a lower dose) in consultation with medical monitor.	• See Section 5.4.8 for management of hyperammonemia.	
Pneumonitis	Grade 2	• Withhold until Grade 0-1. Restart at full dose.	• Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent) followed by taper.	• Monitor subjects for signs and symptoms of pneumonitis. • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Add prophylactic antibiotics for opportunistic infections.
	Grade 3 or 4, or recurrent Grade 2	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.		
Diarrhea/colitis	Grade 2 or 3	• Withhold until Grade 0-1. • Grade 2: Restart at same dose level. • Grade 3: Restart at next dose level lower.	• Administer corticosteroids (initial dose of 1-2 mg/kg/day prednisone or equivalent) followed by taper.	• Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.		

Table 10: Dose Modification and Toxicity Management Guidelines for Adverse Events Related to INCB001158 (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAEv4.03)	Action Taken	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
AST/ALT elevation or increased bilirubin[a]	Grade 2	• Withhold until Grade 0-1. Restart at same dose level.	• Administer corticosteroids (initial dose of 0.5-1mg/kg prednisone or equivalent) followed by taper.	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returns to baseline or is stable.
	Grade 3 or 4	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	
T1DM or hyperglycemia[b]	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	• Withhold until Grade 0-1. • Grade 2: Restart at same dose level. • Grade 3: Restart at next dose level lower.	• Initiate insulin replacement therapy for subjects with T1DM. • Administer antihyperglycemic in subjects with hyperglycemia.	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	• Withhold until Grade 0-1. Restart at same dose level.	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	Grade 3 or 4	• Withhold until Grade 0-1. • Grade 3: Restart at same dose level. • Grade 4: Consider rechallenge at next dose level lower.		
Hyperthyroidism[b]	Grade 2	• Continue.	• Treat with nonselective β-blockers (eg, propranolol) or thionamides as appropriate.	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.		
Hypothyroidism[b]	Grade 2-4	• Continue.	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care.	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	• Withhold until Grade 0-1. Restart at same dose level.	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function.
	Grade 3 or 4	• Withhold until Grade 0-1. • Grade 3: Restart at same dose level. • Grade 4: Consider rechallenge at next dose level lower.		

Table 10: Dose Modification and Toxicity Management Guidelines for Adverse Events Related to INCB001158 (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAEv4.03)	Action Taken	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Rash	Grade 1 or 2	• Continue.	• Manage with topical steroids with or without drug interruption.	
	Grade 3[c]	• Withhold until Grade 0-1. • Restart at same dose level.	• Consider dermatology consultation and biopsy for confirmation of diagnosis. • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	• If toxicity does not resolve within 12 weeks of last dose, or cannot taper below 10 mg or less of prednisone or equivalent within 12 weeks, must permanently discontinue.
	Grade 4	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.	• Dermatology consultation and consideration of biopsy and clinical dermatology photograph. • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	
Asymptomatic[d] amylase or lipase increased	Grade 3	• May continue treatment with medical monitor approval.		• Permanently discontinue if clinical signs and symptoms of pancreatitis develop (abdominal pain, nausea, vomiting). • If toxicity does not resolve within 12 weeks of last dose after an interruption, must permanently discontinue unless approved by the medical monitor to continue. • If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, study drug administration dosing may continue with medical monitor approval.
	Grade 4	• Withhold until Grade 0-1. Restart at same dose level.		
All other irAEs	Grade 3, or intolerable/persistent Grade 2	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.	• Based on severity of AE administer corticosteroids.	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	• Withhold until Grade 0-1. Consider rechallenge at next dose level lower.		

Table 10: Dose Modification and Toxicity Management Guidelines for Adverse Events Related to INCB001158 (Continued)

Adverse Event	Toxicity Grade or Conditions (CTCAEv4.03)	Action Taken	AE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
General Instructions: 1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. 2. For situations where INCB001158 has been withheld, INCB001158 can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. INCB001158 should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. **3.** For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.				

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

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

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

[c] Subjects with Grade 3 rash in the absence of desquamation, with no mucosal involvement, that does not require systemic steroids, and that resolves to Grade 1 within 14 days do not have to hold study medication and may be treated similar as Grade 1 events.

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

5.4.7. Management of Chemotherapy-Related Adverse Events

Dose modifications for hematologic and nonhematologic AEs related to chemotherapy may be managed per institutional guidelines. In the absence of these, recommendations for dose modifications for chemotherapy regimen in the event of hematologic and nonhematologic AEs are provided in the Protocol appendices:

- Appendix C for subjects who receive mFOLFOX6
- Appendix D for subjects who receive gemcitabine/cisplatin
- Appendix E for subjects who receive paclitaxel

It is important to note that some AEs will overlap with potential irAEs. In these cases, both the AE and irAE guidance should be reviewed to determine the most appropriate management of study medications.

5.4.8. Supportive Care Guidelines for Management of Hyperammonemia

Subjects should be monitored for elevated venous plasma ammonia. Asymptomatic clinically significant drug-related elevations in ammonia (eg, a repeatable elevation in ammonia $> 2 \times$ ULN AND $> 2 \times$ baseline) should be managed by interrupting INCB001158 and monitoring to resolution. For symptomatic elevations (ie, significant ammonia elevation associated with nausea, vomiting, severe anorexia, mental status changes, seizure, or other symptoms associated with hyperammonemia), subjects should be admitted for management according to the local institutional protocol for hyperammonemia, including 1) sending appropriate labs (ammonia [on ice, measured immediately], plasma amino acid profile, 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/lactitol, IV Ammonul®), and 5) identifying and treating any potential triggers (eg, discontinue corticosteroids, treat infections, etc).

5.4.9. Criteria for Permanent Discontinuation of Study Drug

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

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

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

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

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

  Note: Consent withdrawn means that the subject can no longer be followed and no additional data can be collected. Subjects may choose to discontinue study treatment and remain in the study to be followed for progression [redacted].

  ***Note*:** As of Protocol Amendment 4, subjects who withdraw consent will no longer be followed for progression [redacted] beyond the last safety follow-up visit.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity (see Sections 5.4.6 and 5.4.9). Subjects with unacceptable toxicities must be withdrawn from study treatment but will continue in the follow-up period of the study (see Section 6.4).
- The subject has an unacceptable toxicity or a toxicity that does not recover in 6 weeks. Investigators who wish to continue treatment after a treatment delay of 4 weeks should consult with the sponsor's medical monitor for approval.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

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

  Note: For unconfirmed progression, see Section 7.7.1.2.

  If, during the course of the study, a subject is found not to have met eligibility criteria (see Section 3), then the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study drug administration in the investigator's opinion, then the sponsor should be consulted for instruction on handling the subject.

5.5.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study drug, the subject will be withdrawn from the study, and the end-of-treatment visit should be conducted. Reasonable efforts should be made to have the subject return for a follow-up visit. These visits are described in Section 6. The last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the eCRF.

If a subject is withdrawn from the study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the eCRF and IRT.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.
- Subjects who discontinue for reasons other than disease progression will continue to be followed for disease status as outlined in Section 6.4.2.

[redacted]

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

5.6. Concomitant Medications

All prior and concomitant medications and treatments must be recorded in the eCRF. Any medication received up to 21 days before the first dose of study treatment and within 90 days after the last dose of study treatment, or until the subject begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered after 90 days after the last dose of study treatment should be recorded for SAEs as defined in Section 8.3. Concomitant treatments/procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

NOTE: As of Protocol Amendment 4, use of concomitant medications should be monitored for subjects to verify that they are not taking any concomitant medication prohibited per protocol; however, concomitant medications no longer need to be collected in the eCRF, except for concomitant medications in relation with SAEs or AESIs.

5.6.1. Permitted Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage frequency, route, and date will also be included on the eCRF.

Palliative and supportive care is permitted during the course of the study for underlying medical conditions and management of symptoms. Surgery for tumor control is not permitted during the study. Palliative radiotherapy is permitted to a limited number of lesions if considered medically necessary by the treating physician as long as the lesions are NOT a RECIST v1.1–defined target lesion. Study therapy should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of study therapy. The specifics of the radiation treatment, including the location, will be recorded.

Xanthine oxidase inhibitors (eg, allopurinol) cause an accumulation of orotic acid in the urine, which would confound the assessment of safety in these subjects. Since there is no expected toxicity associated with this accumulation, subjects receiving xanthine oxidase inhibitors may be enrolled. The sponsor should be informed of any subject that is receiving a xanthine oxidase inhibitor as a concomitant therapy, and the evaluation of urinary orotic acid should not be performed, as the results will be uninterpretable and may incorrectly suggest urea cycle inhibition.

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

5.6.2. Restricted Medications

Caution should be exercised when paclitaxel is administered with concomitant medications that are inhibitors of CYP2C8 and/or CYP3A4, to avoid excess toxicity due to higher paclitaxel exposure.

Caution should be exercised when cisplatin is administered with concomitant medications that are nephrotoxic or ototoxic to avoid additive toxicity with cisplatin.

5.6.3. Prohibited Medications

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

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this Protocol.
- Immunotherapy not specified in this Protocol.
- Investigational agents other than INCB001158 and chemotherapy used in the study.
- Oncologic surgery for tumor control.
- Radiation therapy for disease control.

  Note: Radiation therapy to symptomatic lesions or to the brain may be allowed at the investigator's discretion, provided the lesions were not previously defined by the site as target lesions.
- Live vaccines within 30 days before the first dose of study treatment, while participating in the study, and until 3 months after the last dose of any component of study treatment.
  - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, nasal seasonal flu, nasal H1N1 flu, rabies, Bacillus Calmette-Guérin, and typhoid.
- Except for erythropoietin or darbepoetin alpha (Aranesp®), use of growth factors (G-CSF, GM-CSF, etc) is not permitted in the first treatment cycle unless the subject experiences a hematologic DLT.
- Concomitant treatment with valproic acid/valproate-containing therapies is not permitted, as hyperammonemia is a well-described toxicity of valproic acid, particularly at high exposures, potentially through inhibition of the urea cycle (Verrotti et al 2002, Wadzinski et al 2007).
- Concomitant administration of inducers of CYP2C8 or CYP3A4 is prohibited with paclitaxel treatment. See Appendix F for a list of inducers and inhibitors of CYP2C8 and CYP3A4.
- Prolonged therapy with systemic glucocorticoids (> 7 days) for any purpose other than to modulate symptoms from an AE, SAE, or event of clinical interest, or for use as a premedication for chemotherapy or in participants with a known history of an IV contrast allergy administered as part of CT radiography. Brief, limited use of systemic corticosteroids (≤ 7 days) are permitted where such use is considered standard of care (eg, for chronic obstructive pulmonary disease exacerbation).
  - Replacement doses of steroids (for example, prednisone 5 to 7.5 mg daily) are permitted while on study, as is the use of local steroids.

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

NOTE: As of Protocol Amendment 4, subjects who require the use of a prohibited medication and are removed from treatment will no longer be followed for progression [redacted].

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

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

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (see Table 11, Table 12, Table 13, and Table 14) and all laboratory assessments will be performed as indicated in Table 16. The order of assessments is suggested by the order of mention within the schedule. See Section 7 for instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual.

NOTE: As of Protocol Amendment 4, please refer to Table 15 for the schedule of assessments for all subjects.

Table 11: Schedule of Assessments for Subjects Treated With INCB001158 + mFOLFOX6 or INCB001158 + Paclitaxel

Procedure	Protocol Section	Screening	Treatment (28-Day Cycles)							EOT	Follow-Up				Notes
			Cycle 1			Other Cycles					Safety		Disease Status	[redacted]	
		Days -21 to -1	D1	D8 ± 3d	D15 ± 3d	D1 ± 3d	D8 ± 3d	D15 ± 3d	Q8W ± 7d	+ 7d	30 d After EOT ± 7d	90 d After EOT ± 7d	Q8W After EOT ± 7d	[redacted]	
Administrative procedures															
Informed consent	7.1	X													
Review inclusion and exclusion criteria	3	X	X												
Demography and medical history	7.3	X													
Prior/concomitant medications	7.4	X	X	X	X	X		X		X	X	X	X		
Dispensing INCB001158 study drug	5.1.1		X			X									
Study treatment administration															
Administer INCB001158 at site	5.2.1		X	X	X	X	X*	X							Subject to withhold AM dose of INCB001158 study drug. * D8 of Cycle 2 and beyond only for subjects receiving paclitaxel.
Administer mFOLFOX6 at site	5.2.2		X		X	X		X							Should be administered after INCB001158.
Administer paclitaxel at site	5.2.4		X	X	X	X	X	X							Should be administered after INCB001158.
Assess study drug compliance	5.3					X				X					
Distribute reminders	7.11.1	X	X	X	X	X	X*	X		X					* D8 of Cycle 2 and beyond for subjects receiving paclitaxel.
Clinical procedures and assessments															
Comprehensive physical examination	7.6.2.1	X													
Targeted physical examination	7.6.2.2		X	X	X	X		X		X	X	X	X		

Table 11: Schedule of Assessments for Subjects Treated With INCB001158 + mFOLFOX6 or INCB001158 + Paclitaxel (Continued)

Procedure	Protocol Section	Screening	Treatment (28-Day Cycles)							EOT	Follow-Up				Notes
			Cycle 1			Other Cycles					Safety		Disease Status	[redacted]	
		Days -21 to -1	D1	D8 ± 3d	D15 ± 3d	D1 ± 3d	D8 ± 3d	D15 ± 3d	Q8W ± 7d	+ 7d	30 d After EOT ± 7d	90 d After EOT ± 7d	Q8W After EOT ± 7d	[redacted]	
Vital signs	7.6.3	X	X*	X	X*	X		X		X	X	X	X		* Orthostatic blood pressure monitoring at predose and 4 hours postdose.
12-lead ECG	7.6.4	X	X*	X*						X					* Timed triplicate ECGs (separated by 5 minutes ± 1 minute) at predose and 2 to 4 hours postdose.
ECOG status	7.8.1	X	X	X	X	X	X*	X		X	X		X		* D8 of Cycle 2 and beyond only for subjects receiving paclitaxel.
Radiographic tumor assessments (CT or MRI)	7.7.1	X							X*	X**			X		* Baseline and then every 8 weeks ± 7 days. ** ± 4 weeks.
Review AEs	8.1	X	X	X	X	X	X*	X		X	X	X	X		* D8 of Cycle 2 and beyond only for subjects receiving paclitaxel.
Post-treatment anticancer therapy status	7.5										X	X	X	[redacted]	
[redacted]	[redacted]													[redacted]	

Table 12: Schedule of Laboratory Assessments for Subjects Treated With INCB001158 + mFOLFOX6 or INCB001158 + Paclitaxel

Procedure	Protocol Section	Screening	Treatment (28-Day Cycles)							EOT	Safety Follow-Up		Notes
			Cycle 1			Other Cycles							
		Days -21 to -1	D1	D8 ± 3d	D15 ± 3d	D1 ± 3d	D8 ± 3d	D15 ± 3d	Q8W ± 7d	+ 7d	30 d After EOT ± 7d	90 d After EOT ± 7d	
Local laboratory tests													
Chemistries	7.6.5.1	X	X*	X	X	X	X**	X		X	X	X	* Does not need to be repeated if the screening sample was obtained within 3 days before C1D1, unless a clinically significant change is suspected. ** D8 of Cycle 2 and beyond only for subjects receiving paclitaxel.
Hematology	7.6.5	X	X*	X	X	X	X**	X		X	X	X	
Coagulation panel	7.6.5.7	X									X		
Hepatitis and HIV screening	7.6.5.6	X											
Urinalysis	7.6.5.2	X	X*			X					X		* Does not need to be repeated if the screening sample was obtained within 3 days before C1D1, unless a clinically significant change is suspected.
Blood sample for plasma ammonia levels	7.6.5.3	X											Collect during screening. If plasma ammonia is above ULN, repeat screening sample to confirm value. If the subject experiences an elevation in urine orotic acid (> 10 × ULN fasted or > 40 × ULN of any value) while on study treatment or during the follow-up period, monitor plasma ammonia levels each time the urine orotic acid is tested, at least until orotic acid levels have returned to normal, at the investigator's and medical monitor's discretion.
CA 125 testing (OC only)	7.6.5.5	X	X			X*			X	X			*Collect at C2D1 and C4D1. If available, the most recent measurement before screening should be recorded.
Pregnancy test	7.6.5.4	X	X*			X*					X		All female subjects of childbearing potential. *Day 1 of each cycle.

Table 12: Schedule of Laboratory Assessments for Subjects Treated With INCB001158 + mFOLFOX6 or INCB001158 + Paclitaxel (Continued)

Procedure	Protocol Section	Screening	Treatment (28-Day Cycles)							EOT	Safety Follow-Up		Notes
			Cycle 1			Other Cycles							
		Days -21 to -1	D1	D8 ± 3d	D15 ± 3d	D1 ± 3d	D8 ± 3d	D15 ± 3d	Q8W ± 7d	+ 7d	30 d After EOT ± 7d	90 d After EOT ± 7d	
Central laboratory samples													
Urine sample for orotic acid	7.6.5.2		X*	X*	X*	X*							* See Table 17 for sample timings. Additional samples may be collected as clinically indicated.
Blood sample for INCB001158 PK	7.9.1		X*			X*							* See Table 20 and Table 21 for detailed for extensive and sparse sample timings. Samples will be drawn on C1D1 and C2D1 only.
[redacted]													

Table 12: Schedule of Laboratory Assessments for Subjects Treated With INCB001158 + mFOLFOX6 or INCB001158 + Paclitaxel (Continued)

Procedure	Protocol Section	Screening	Treatment (28-Day Cycles)							EOT	Safety Follow-Up		Notes
			Cycle 1			Other Cycles							
		Days -21 to -1	D1	D8 ± 3d	D15 ± 3d	D1 ± 3d	D8 ± 3d	D15 ± 3d	Q8W ± 7d	+ 7d	30 d After EOT ± 7d	90 d After EOT ± 7d	
[redacted]													

Table 13: Schedule of Assessments for Subjects Treated With INCB001158 + Gemcitabine and Cisplatin

Procedure	Protocol Section	Screening	Treatment (21-Day Cycles)						Follow-Up				
			Cycle 1			Other Cycles				Safety		Disease Status	[redacted]
		Days -21 to -1	D1	D8 ± 3d	D15 ± 3d	D1 ± 3d	D8 ± 3d	Q8W ± 7d	EOT + 7d	30 d After EOT ± 7d	90 d After EOT ± 7d	Q8W After EOT ± 7d	[redacted]
Administrative procedures													
Informed consent	7.1	X											
Review inclusion and exclusion criteria	3	X	X										
Demography and medical history	7.3	X											
Prior/concomitant medications	7.4	X	X	X	X	X			X	X	X	X	
Dispensing INCB001158 study drug	5.1.1		X			X							
Study treatment administration													
Administer INCB001158 at site	5.2.1		X	X	X	X	X						Subject to withhold AM dose of INCB001158 study drug.
Administer cisplatin/ gemcitabine at site	5.2.3		X	X		X	X						Should be administered after INCB001158.
Assess study drug compliance	5.3					X			X				
Distribute reminders	7.11.1	X	X	X	X	X	X		X				
Clinical procedures and assessments													
Comprehensive physical examination	7.6.2.1	X											
Targeted physical examination	7.6.2.2		X	X	X	X			X	X	X	X	
Vital signs	7.6.3	X	X*	X	X*	X			X	X	X	X	* Orthostatic blood pressure monitoring at predose and 4 hours postdose.

Table 13: Schedule of Assessments for Subjects Treated With INCB001158 + Gemcitabine and Cisplatin (Continued)

Procedure	Protocol Section	Screening	Treatment (21-Day Cycles)						EOT	Follow-Up				Notes
			Cycle 1			Other Cycles				Safety		Disease Status	[redacted]	
		Days -21 to -1	D1	D8 ± 3d	D15 ± 3d	D1 ± 3d	D8 ± 3d	Q8W ± 7d	EOT + 7d	30 d After EOT ± 7d	90 d After EOT ± 7d	Q8W After EOT ± 7d	[redacted]	
12-lead ECG	7.6.4	X	X*	X*					X					* Timed triplicate ECGs (separated by 5 minutes ± 1 minute) at predose and 2 to 4 hours postdose.
ECOG status	7.8.1	X	X	X	X	X	X		X	X		X		
Radiographic tumor assessments (CT or MRI)	7.7.1	X						X*	X**			X		* Baseline and then every 8 weeks ± 7 days. ** ± 4 weeks.
Review AEs	8.1	X	X	X	X	X	X		X	X	X	X		
Post-treatment anticancer therapy status	7.5									X	X	X	[redacted]	
[redacted]	[redacted]												[redacted]	

Table 14: Schedule of Laboratory Assessments for Subjects Treated With INCB001158 + Gemcitabine and Cisplatin

Procedure	Protocol Section	Screening	Treatment (21-Day Cycles)						EOT	Safety Follow-Up		Notes
			Cycle 1			Other Cycles						
		Days -21 to -1	D1	D8 ± 3d	D15 ± 3d	D1 ± 3d	D8 ± 3d	Q8W ± 7d	+ 7d	30 d After EOT ± 7d	90 d After EOT ± 7d	
Local laboratory tests												
Chemistries	7.6.5.1	X	X*	X	X	X	X		X	X	X	* Does not need to be repeated if the screening sample was obtained within 3 days before C1D1, unless a clinically significant change is suspected.
Hematology	7.6.5	X	X*	X	X	X	X		X	X	X	
Coagulation panel	7.6.5.7	X								X		
Hepatitis and HIV screening	7.6.5.6	X										
Urinalysis	7.6.5.2	X	X*			X				X		* Does not need to be repeated if the screening sample was obtained within 3 days before C1D1, unless a clinically significant change is suspected.
Blood sample for plasma ammonia levels	7.6.5.3	X										Collect during screening. If plasma ammonia is above ULN, repeat screening sample to confirm value. If the subject experiences an elevation in urine orotic acid (> 10 × ULN fasted or > 40 × ULN of any value) while on study treatment or during the follow-up period, monitor plasma ammonia levels each time the urine orotic acid is tested, at least until orotic acid levels have returned to normal, at the investigator's and medical monitor's discretion.
CA 125 testing (OC only)	7.6.5.5	X	X			X*		X	X			*Collect at C2D1 and C4D1. If available, the most recent measure before screening should be recorded.
Pregnancy test	7.6.5.4	X	X*			X*				X		All female subjects of childbearing potential. *Day 1 of each cycle.

Table 14: Schedule of Laboratory Assessments for Subjects Treated With INCB001158 + Gemcitabine and Cisplatin (Continued)

Procedure	Protocol Section	Screening	Treatment (21-Day Cycles)						EOT	Safety Follow-Up		Notes
			Cycle 1			Other Cycles						
		Days -21 to -1	D1	D8 ± 3d	D15 ± 3d	D1 ± 3d	D8 ± 3d	Q8W ± 7d	+ 7d	30 d After EOT ± 7d	90 d After EOT ± 7d	
Central laboratory samples												
Urine sample for orotic acid	7.6.5.2		X*	X*	X*	X*						* See Table 17 for sample timings. Additional samples may be collected as clinically indicated.
Blood sample for INCB001158 PK	7.9.1		X*			X*						* See Table 20 and Table 21 for detailed for extensive and sparse sample timings. Samples will be drawn on C1D1 and C2D1 only.
[redacted]												

Table 14: Schedule of Laboratory Assessments for Subjects Treated With INCB001158 + Gemcitabine and Cisplatin (Continued)

Procedure	Protocol Section	Screening	Treatment (21-Day Cycles)						EOT	Safety Follow-Up		Notes
			Cycle 1			Other Cycles						
		Days -21 to -1	D1	D8 ± 3d	D15 ± 3d	D1 ± 3d	D8 ± 3d	Q8W ± 7d	+ 7d	30 d After EOT ± 7d	90 d After EOT ± 7d	
[redacted]												

Table 15: Schedule of Assessments for All Subjects (as of Protocol Amendment 4)

Procedure	Protocol Section	Treatment Period (21- or 28-Day Cycle)	EOT + 7d	Safety Follow-Up 30 d After EOT ± 7d	Safety Follow-Up 90 d After EOT ± 7d	Notes
Informed consent	7.1	X				Subjects will sign a new ICF as per Protocol Amendment 4.
Concomitant medications	7.4	X	X	X	X	Review to ensure no prohibited medications are being used. Provide data to sponsor about medications used for SAEs and AESIs only.
Dispense/Administer INCB001158	5.2.1	X				On clinic days when subjects are receiving chemotherapy at the site, INCB001158 should be administered before beginning the infusion of the chemotherapy.
Administer chemotherapy regimen at site	5.2.2 5.2.3 5.2.4	X*				Should be administered after INCB001158. *Refer to the applicable chemotherapy administration as per the subject's treatment assignment (Section 5.1.1).
Assess study drug compliance	5.3	X*	X			*Day 1 of each cycle.
Distribute reminders	7.11.1	X*	X			*On the clinic days for the next visit.
AE assessment	8.1	X	X	X	X	All SAEs and AESIs must be recorded in the eCRFs, regardless of the causal relationship.
Radiographic tumor assessments (CT/MRI)	7.7	X*	X			*Every 8 weeks ± 7 days. After Week 96, the radiographic tumor assessments are only required to be performed as per standard of care guidelines for the subject's condition and monitoring.
Pregnancy test	7.6.5.4	X*		X		All female subjects of childbearing potential. *Day 1 of each cycle.
Post-treatment anticancer therapy status	7.5			X	X	If a subject is scheduled to begin a post-treatment anticancer therapy before the end of the safety follow-up period, then the safety follow-up visit should be performed before post-treatment anticancer therapy is started.

Table 16: Laboratory Tests: Required Analytes

Chemistries	Hematology	Urinalysis With Microscopic Examination	Hepatitis and HIV Screening
Albumin Alkaline phosphatase ALT Amino acid panel[a] Ammonia Amylase Arginase[a] AST Bicarbonate or CO_2 Blood urea nitrogen or urea Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipase Ornithine[a] Phosphate Potassium Sodium Thyroid panel: TSH, FT4, FT3/T3 Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid	Complete blood count, including: Hemoglobin Hematocrit Platelet count Red blood cell count White blood cell count Differential count, including: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Absolute values must be provided for: WBC differential laboratory results: Lymphocytes Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Orotic acid[a] Protein Urobilinogen	Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis B core antibody HBV-DNA HCV antibody HCV-RNA HIV-RNA (if required by local regulations)
		Lipid Panel	**Pregnancy Testing**
		Total cholesterol Triglycerides LDL HDL	Female subjects of childbearing potential require a serum pregnancy test at screening and a urine pregnancy test before the first dose on Cycle 1 Day 1 and on Day 1 of every cycle. A serum pregnancy test will be performed at 30-day safety follow up visit. Pregnancy tests (serum or urine) should be repeated if required by local regulations.
		Coagulation	
		PT aPTT INR	
		CA 125 testing (subjects with OC only)	

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

6.1. Screening

Screening is the interval between signing the ICF and the day the subject is enrolled in the study (Cycle 1 Day 1). Screening may not exceed 21 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

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

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be

in error. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to determine subject eligibility. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status (eg, after recovery from an infection).

6.2. Treatment

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

Subjects will have regularly scheduled study visits as outlined in Table 11, Table 12, Table 13, and Table 14 (see Table 15 for all subjects as of Protocol Amendment 4), and toxicities will be monitored continuously and will be graded using the NCI CTCAE v4.03 criteria.

6.3. End of Treatment

When the subject permanently discontinues treatment, as outlined in Section 5.5, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The EOT visit may occur up to 7 days after the subject receives the final dose of study treatment. The subject should be encouraged to return for the safety follow-up visit. When the subject permanently discontinues study drug, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The subject should be encouraged to return for the follow-up visit.

6.4. Follow-Up

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 days and 90 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 90 days after the last dose of study drug, the date of the second safety 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 subject return for the follow-up visits and report any AEs that may occur during this period. If the subject cannot return to the site for the safety follow-up visits, the subject should be contacted by telephone for assessment of AEs and SAEs, and this should be documented in the eCRF.

Adverse events and SAEs before the start of the new anticancer therapy must be reported. If a subject begins a new anticancer therapy before the end of the 30-day or 90-day safety follow-up

period, the safety follow-up visit should be performed before the new anticancer therapy is started.

[redacted]

NOTE: As of Protocol Amendment 4, data will only be collected for SAEs, AESIs, and pregnancy. [redacted]

6.4.2. Disease Status Follow-Up

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

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

Information regarding post-treatment anticancer therapy will be collected if it is initiated.

NOTE: As of Protocol Amendment 4, disease status follow-up visits for subjects who discontinue study treatment for a reason other than disease progression are no longer required beyond the last safety follow-up visit. The last disease status follow-up data will be recorded in the eCRF at the time of the last safety follow-up visit. The last study visit will be the safety follow-up visit.

[redacted]

6.5. End of Study

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

- Subject dies and a date of death is available.
- Subject is known to have died; however, the date of death cannot be obtained. (NOTE: Every effort must be made to obtain the date of death.)
- Consent is withdrawn for any further contact related to this study.
  - Subjects may choose to withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled. Every reasonable effort should be made to determine the reason a subject withdraws prematurely, and this information should be recorded in the eCRF.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB or IEC.

6.6. Unscheduled Visits

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

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

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

7.2. Interactive Response Technology Procedure

The IRT will be contacted to obtain a subject identification number when a subject enters screening. Upon determining that the subject is eligible for study entry, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at each regular study visit to update the study drug supply.

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

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

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication history will be collected at screening. In addition, disease-relevant biomarker information is required where available (eg, CRC: MSI status, carcinoembryonic antigen level; gastric cancer: Epstein Barr virus status, *H. pylori* status, CA 19-9 level; OC: BRCA1 and BRCA2 status, CA 125 level; EC: MSI status). These items will be recorded separately and not listed in medical history.

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. All concomitant medications and measures must be recorded in the eCRF, and any medication received or procedure performed within 21 days before enrollment and up to the end of study will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be

recorded in the eCRF. See Section 5.6 for details regarding restricted and prohibited medications.

NOTE: As of Protocol Amendment 4, use of concomitant medications should be monitored for subjects to verify that they are not taking any concomitant medication prohibited per protocol; however, concomitant medications no longer need to be collected in the eCRF, except for concomitant medications in relation with SAEs or AESIs.

7.5. Post-Treatment Anticancer Therapy Status

The investigator or qualified designee will review all new antineoplastic therapy initiated after the last dose of study treatment. If a subject initiates a new anticancer therapy within 30 days after the last dose of study treatment, then the 30-day safety follow-up visit should occur before the first dose of the new anticancer therapy.

7.6. Safety Assessments

The chemotherapy agents used in this study are approved therapies; therefore, the investigator should refer to and follow the safety management guidelines as appropriate within the prescribing information for the chemotherapy agents.

NOTE: As of Protocol Amendment 4, safety assessments are only required to be performed as per the site standard of care guidelines for the subject's condition and monitoring. Only SAEs, AESIs, and pregnancy will be collected in the eCRF.

7.6.1. Adverse Events

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

7.6.2. Physical Examinations

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

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

7.6.2.1. Comprehensive Physical Examination

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

7.6.2.2. Targeted Physical Examination

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

7.6.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the subject in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. In addition, orthostatic blood pressure monitoring will be performed on the days indicated in Table 11 and Table 13. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.6.4. Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.6.5. Laboratory Assessments

A certified laboratory local to the study site and subject will perform most of the clinical laboratory assessments for safety (ie, chemistries, hematology assessments, coagulation panel, thyroid panel, lipid panel, and urinalysis). The investigative site will enter the laboratory results and laboratory normal ranges into the eCRF. All local laboratory assessments should be performed using standard procedures on the days indicated in Table 12 and Table 14. Table 16 lists the specific laboratory analytes required for each test. Some additional tests (ie, plasma arginase, amino acid panel, including ornithine, plus urinary orotic acid – see Table 17) will be conducted by 1 or more central laboratories, on the days indicated in Table 12 and Table 14.

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

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

NOTE: As of Protocol Amendment 4, laboratory assessments should be performed in accordance with the standard of care of the investigational site for the subject's condition. Laboratory results do not need to be reported in the eCRF, but all laboratory results

corresponding with an SAE or an AESI will be reported on the SAE form. In addition, pregnancy testing will continue to be performed for all subjects as per the schedule of assessments in Table 15.

7.6.5.1. Chemistries

In addition to the standard serum chemistry analytes, [redacted] as outlined in Table 16.

[redacted]

See Table 12 and Table 14 for sampling timepoints and the Laboratory Manual for details of how to process, store, and ship the samples to the certified central laboratory or laboratories for sample analysis.

7.6.5.2. Urinalysis

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

Table 17: Sample Collection Time Windows for Urine Assessments of Orotic Acid

Study Visit	Time
C1D1	Predose and 6 h postdose
C1D8	Predose
C1D15	Predose and 6 h postdose
C2D1 and D1 of all subsequent cycles	Predose

Note: Additional samples may be collected as clinically indicated.

7.6.5.3. Plasma Ammonia

Plasma ammonia levels are to be tested during screening (Table 12 and Table 14). If above the ULN, repeat the sample to confirm the value. If the subject experiences an elevation in urine orotic acid (> 10 × ULN fasted or > 40 × ULN of any value) while on study treatment or during the follow-up period, monitor plasma ammonia levels each time the urine orotic acid is tested, at least until orotic acid levels have returned to normal, at the investigator's and medical monitor's discretion.

7.6.5.4. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening. A urine pregnancy test will be required on Cycle 1 Day 1 (before the first dose of study drug) and Day 1 of each subsequent cycle (Table 12 and Table 14; Table 15 for all subjects as of Protocol Amendment 4). A serum pregnancy test should also be repeated at the 30-day

safety follow-up visit. Pregnancy testing is not required if a subject is going to hospice. Urine pregnancy tests will be conducted as medically indicated, or per country-specific requirement. Urine pregnancy tests will be performed locally. If a urine pregnancy test is positive, then the results should be confirmed with a serum pregnancy test.

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

7.6.5.5. CA 125 Monitoring

CA 125 monitoring will be performed locally for subjects with OC as indicated in Table 12 and Table 14. If available, the most recent measure before screening will also be recorded.

7.6.5.6. Hepatitis and HIV Screening Tests

Hepatitis and HIV screening assessments will be performed at the screening visit (Table 12 and Table 14) to rule out hepatitis and HIV infection, respectively; required analytes are shown in Table 16. Generally, hepatitis and HIV tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

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

7.6.5.7. Coagulation Panel

A coagulation panel will be performed as indicated in Table 12 and Table 14; required analytes for this panel are listed in Table 16. The coagulation panel will be analyzed by the site's local laboratory.

7.7. Efficacy Assessments

NOTE: As of Protocol Amendment 4, no further efficacy assessment will be required beyond Week 96. After Week 96, the radiographic tumor assessments are only required to be performed as per the site standard of care guidelines for the subject's condition and monitoring. Subjects must be withdrawn from the study if, in the opinion of the investigator, the disease has progressed and the subject is no longer having clinical benefit from the study treatment.

7.7.1. Tumor Imaging and Assessment of Disease

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

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

The sponsor may request that images from scans obtained during the study be sent to a central reader for independent image analysis.

7.7.1.1. Initial Tumor Imaging

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

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 21 days prior to the date of enrollment.

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

7.7.1.2. Tumor Imaging During the Study

The first on study imaging assessment should be performed at 8 weeks (56 days ± 7 days) from the date of enrollment. Imaging then continues every 8 weeks (56 days ±7 days). This equates to an imaging schedule occurring after Weeks 8, 16, 24, 32, 40, etc. Imaging timing should follow calendar days and should not be adjusted for delays in cycle dosing.

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

Partial response and CR should be confirmed by a repeat imaging assessment. The imaging for confirmation of response may be performed no earlier than 4 weeks after the first indication of a response, or at the next scheduled scan (ie, 8 weeks later), whichever is clinically indicated. Subjects will then return to the regular imaging schedule, starting with the next scheduled imaging timepoint. Subjects who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging timepoint.

[redacted]

[redacted]

7.7.1.3. End-of-Treatment and Follow-Up Imaging

In subjects who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 week window). If a previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. [redacted]

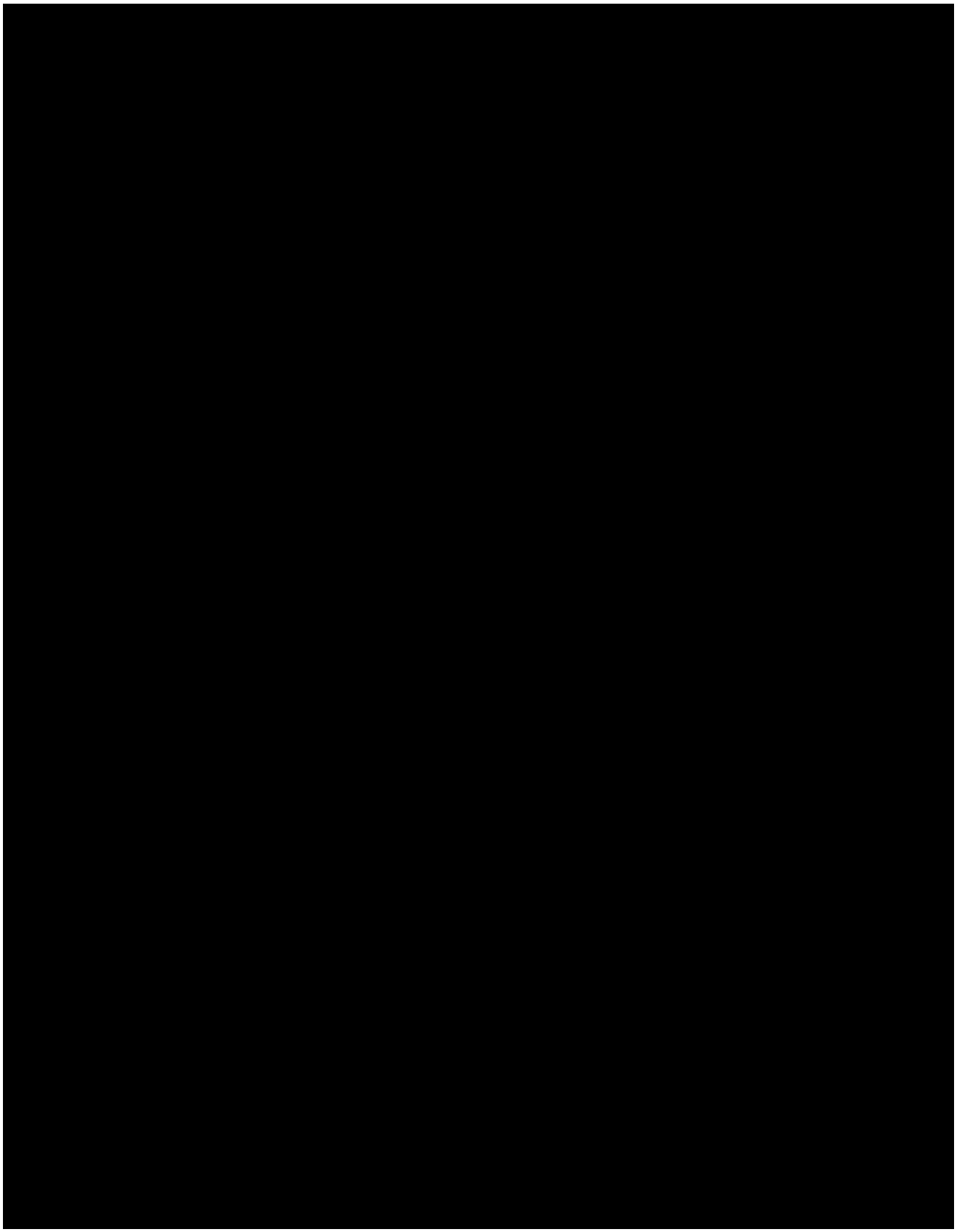
In subjects who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment until the start of new anti-cancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first. For these subjects, the next imaging would occur at the discontinuation visit. If previous imaging was obtained within 4 weeks before the date of discontinuation, then imaging at treatment discontinuation is not mandatory. The next imaging would then occur every 8 weeks (± 7 days) subsequently. [redacted]

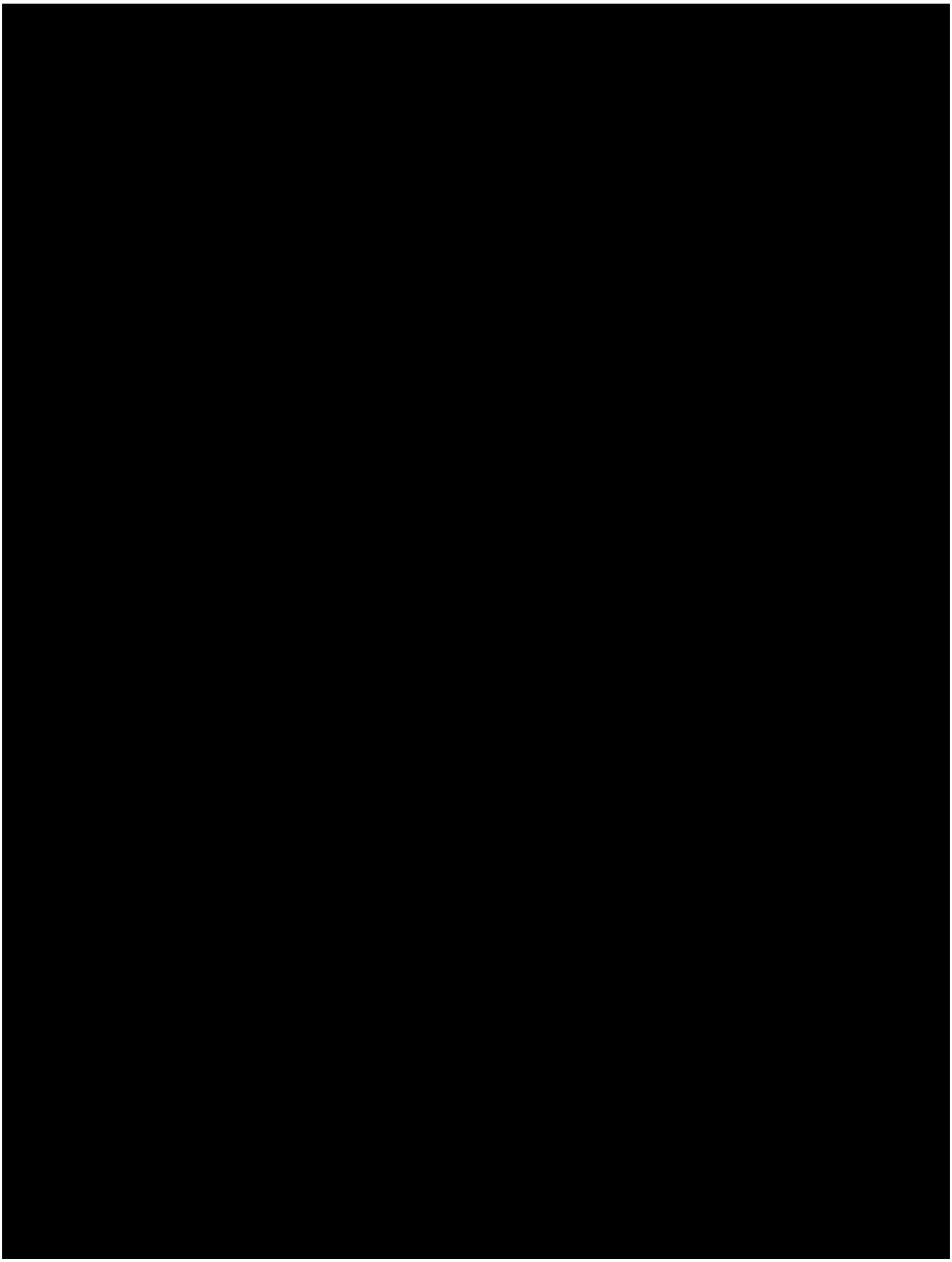
NOTE: As of Protocol Amendment 4, follow-up imaging to monitor disease status for subjects who discontinue study treatment for any of the aforementioned reasons is no longer required beyond the last safety follow-up visit (see Section 6.4.2).

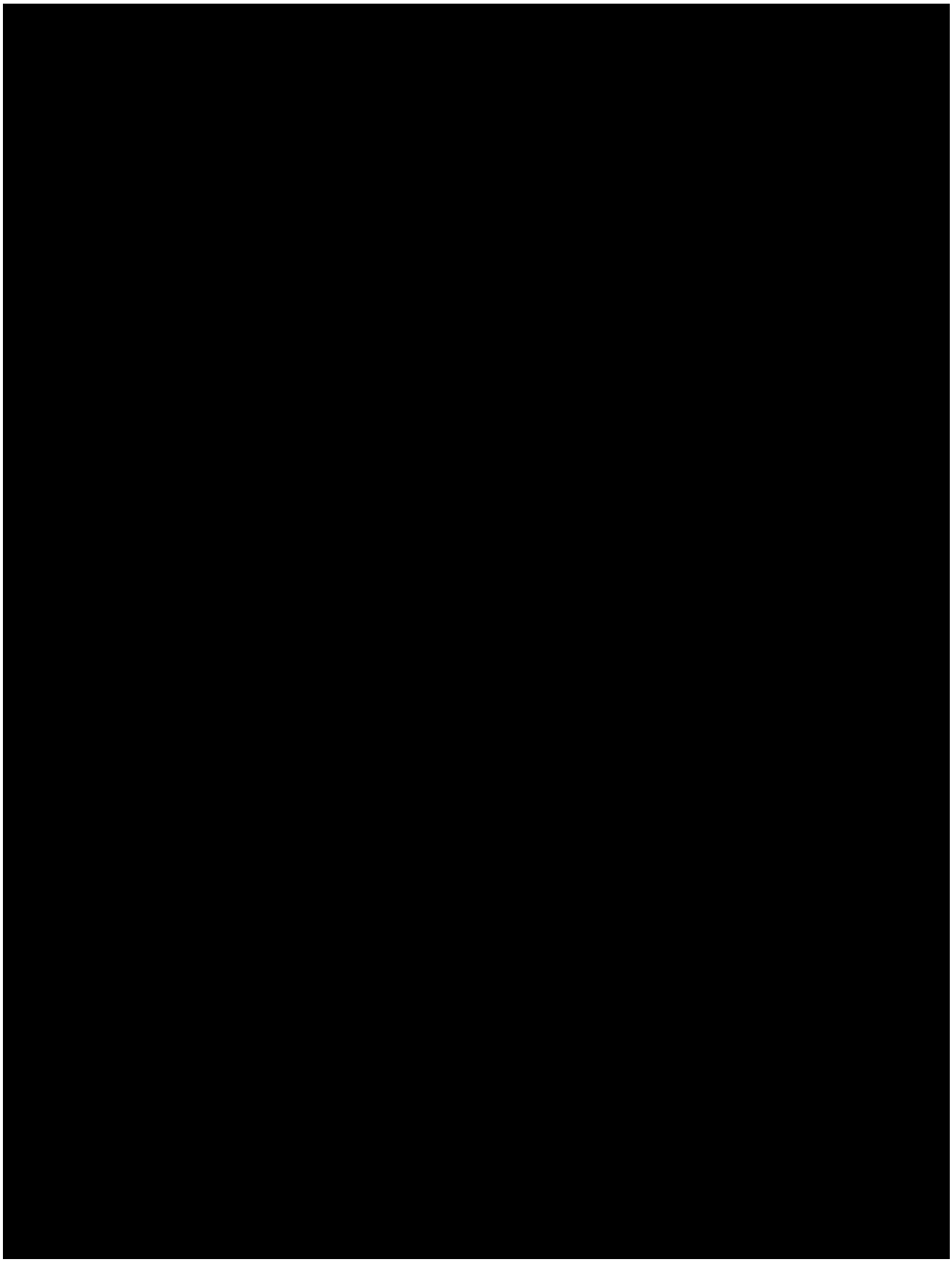
7.7.1.4. RECIST v1.1 Assessment of Disease

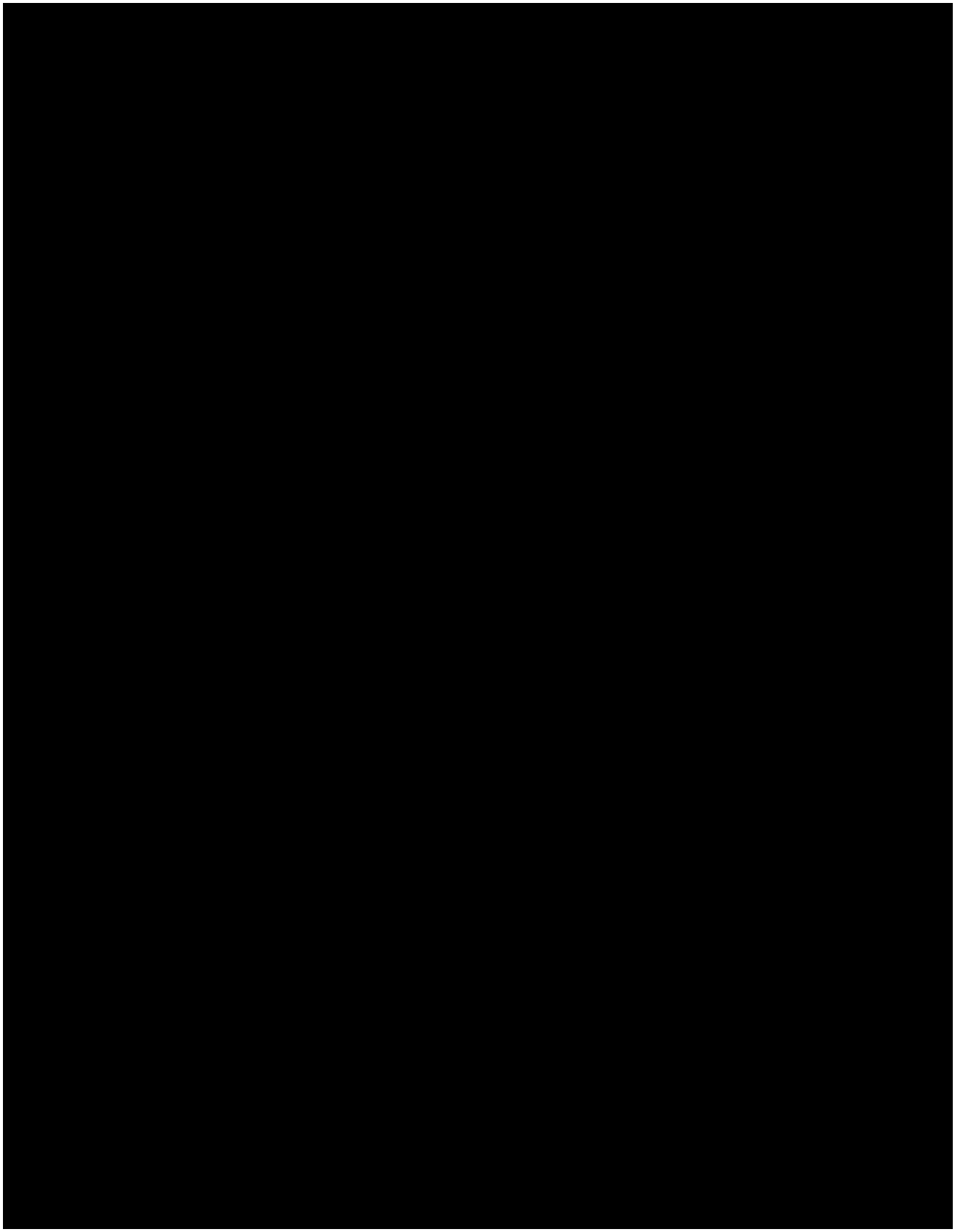
RECIST v1.1 will be the primary measure for assessment of tumor response and as a basis for Protocol guidelines related to disease status (eg, discontinuation of study therapy).

[redacted]









7.8. Performance and Quality-of-Life Assessments

7.8.1. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status will be assessed as shown in Table 11 and Table 13 according to the criteria in Table 19.

Table 19: Eastern Cooperative Oncology Group Performance Status Scoring

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

Source: Oken et al 1982.

7.9. Pharmacokinetic Assessments

7.9.1. Blood Sample Collection

Subjects will arrive at the clinic having fasted at least 8 hours and having withheld their morning dose of INCB001158. Pharmacokinetic samples will be obtained at the visits indicated in Table 12 and Table 14. **Predose is defined as within 24 hours before administration of the morning dose of INCB001158 and before administration of chemotherapy (if drugs are given on PK assessment days)**. After the predose PK sample is drawn, subjects will take INCB001158 and then chemotherapy. [redacted] The exact date and time of the PK blood draws will be recorded in the eCRF along with the date and time of the last dose of study drug and details of the last meal preceding the blood draw. Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Sample collection times and windows for INCB001158 are shown in Table 20 and Table 21.

Table 20: Extensive Sample Collection Time Windows for Pharmacokinetic Assessments for INCB001158 in the First 12 Subjects Enrolled in Each Chemotherapy Regimen in Phase 2

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

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

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

7.9.2. Bioanalytical Methodology and Analysis

The plasma samples will be analyzed for INCB001158 by using a validated liquid chromatography tandem mass spectrometry assay. These samples will be analyzed by the sponsor or its designee.

[redacted]

[redacted]

7.11. Other Study Procedures

7.11.1. Distribution of Subject Reminder Cards and/or Subject Diaries

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

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

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

[redacted]

[redacted]

8. SAFETY MONITORING AND REPORTING

NOTE: As of Protocol Amendment 4, the only safety data that will be collected will be related to SAEs, AESIs, and pregnancy. The safety follow-up visits may be completed remotely (such as by televisit).

8.1. Adverse Events

8.1.1. Definitions

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

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 90 days after the last dose of study drug. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

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

[redacted]

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

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

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

- The severity grade (CTCAE Grade 1 to 5).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no). Relatedness will be assessed for INCB001158 and chemotherapy.
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in Section 8.3.1.

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

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

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

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example,

2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE, that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

NOTE: As of Protocol Amendment 4, all AESIs will continue to be reported in the eCRF.

8.2. Laboratory Test Abnormalities

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

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.5) and should not contribute to the designation of a laboratory test abnormality as an SAE.

NOTE: As of Protocol Amendment 4, laboratory assessments should be performed in accordance with the standard of care of the investigational site for the subject's condition. Laboratory results do not need to be reported in the eCRF, but all laboratory results corresponding with an SAE or AESI will be reported on the SAE form.

8.3. Serious Adverse Events

8.3.1. Definitions

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

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

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

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 90 days after the last dose of study drug, whichever is later) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Any SAEs occurring more than 90 days after the last dose of study drug should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study drug.

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to the study treatment. Relatedness will be assessed for INCB001158 and chemotherapy.

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

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

Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or subject disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any

study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

NOTE: As of Protocol Amendment 4, all SAEs regardless of causality relationship will continue to be reported in the eCRF.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure subject safety:

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

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

NOTE: As of Protocol Amendment 4, pregnancy will continue to be reported in the eCRF.

8.6. Warnings and Precautions

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

8.7. Product Complaints

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

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

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

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

9. STATISTICS

9.1. Study Populations

The full analysis set includes all subjects enrolled in the study who received at least 1 dose of study treatment (INCB001158, mFOLFOX6, gemcitabine/cisplatin, or paclitaxel). This population will be used in the analyses of demographic, baseline, safety, study treatment administration, and efficacy data.

The DLT evaluable population is defined in Section 5.4.2 and includes subjects who receive at least 32 of 42 doses for 21-day cycle regimens and at least 42 of 56 doses for 28-day cycle regimens (both representing ≥ 75% of the dose planned) of INCB001158 at the level assigned or have a DLT. This population will be used for determining tolerability of the dose.

The PK evaluable population includes subjects who received at least 1 dose of study treatment (INCB001158, mFOLFOX6, gemcitabine/cisplatin, or paclitaxel) and had at least 1 postdose PK sample collected and analyzed. [redacted]

9.2. Selection of Sample Size

9.2.1. Sample Size for Phase 1

In Phase 1, the BOIN design will be used to determine the RP2D of INCB001158 when given in combination with chemotherapy in subjects with advanced or metastatic solid tumors. The details of the dose escalation, de-escalation, and elimination rules according to the BOIN design are provided in Section 4.1.1.

9.2.2. Sample Size for Phase 2

Phase 2 will further evaluate the safety, tolerability, preliminary efficacy, PK, and pharmacologic activity of the recommended dose of INCB001158 in combination with chemotherapy. A Simon 2-stage design will be run for each tumor type within a given expansion cohort.

The sample size for each tumor type within a given expansion cohort will be guided by the Simon 2-stage design. The planned Simon 2-stage designs are summarized in Table 7. Each Simon 2-stage design will have a stopping rule to allow early termination of a particular tumor type within the given cohort at the end of Stage 1 if there is insufficient response observed, while enrolling enough subjects to predict possible target responses worthy of cohort expansion and potentially further evaluation in future studies. The individual Simon 2-stage designs run for each tumor type within each cohort will have design parameters that are determined by historical response rates.

In order to determine whether the target response rate (p_1%) is likely, an initial number of evaluable subjects (n_1 subjects) will be treated at the RP2D of INCB001158 in combination with each chemotherapy (Stage 1). If there are r_1 or fewer responses in the expansion cohort, then it will be concluded that the true response rate is unlikely to be ≥ the target rate, and no more subjects will be enrolled in that tumor type for that cohort in Stage 2. In the cohorts in which $> r_1$ responses are observed among the Stage 1 subjects, n_2 additional evaluable subjects will be

treated in Stage 2 to estimate the response rate. At the end of Stage 2, if $\leq r$ subjects have responded among the n evaluable subjects, then the drug will be declared nonpromising for that cohort. The detailed calculations for each tumor type–specific cohort are based on a 1-sided Type I error of 0.1 and power of 80%.

9.3. Level of Significance

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

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

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

9.4.1.2. Secondary Efficacy Analyses

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

- ORR, defined as the percentage of subjects having a CR or PR, as determined by investigator assessment of radiographic disease as per RECIST v1.1 (Phase 1 only).
- DOR, defined as the time from earliest date of CR or PR (as determined by investigator assessment of radiographic disease assessment per RECIST v1.1) until the earliest date of disease progression or death due to any cause, if occurring sooner than disease progression.
- DCR, defined as the percentage of subjects having CR, PR, or SD for at least 8 weeks, as determined by investigator assessment of radiographic disease as per RECIST v1.1.
- PFS, defined as the time from date of first dose of study drug until the earliest date of disease progression (as determined by investigator assessment of radiographic disease assessment per RECIST v1.1), or death due to any cause, if occurring sooner than progression.

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

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

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

9.4.2.2. Clinical Laboratory Tests

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

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

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

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

9.4.2.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 22), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 22: Criteria for Clinically Notable Vital Sign Abnormalities

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

9.4.2.4. Electrocardiograms

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

Table 23: Criteria for Clinically Notable Electrocardiogram Abnormalities

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

QTcF = Fridericia correction.

9.4.2.5. Adverse Events of Special Interest

Adverse events of special interest include irAEs that are seen with immunotherapy and any other observed autoimmune phenomenon.

An overall summary of irAEs will include number (%) of subjects reporting any irAEs, any Grade 3 or higher irAEs, any treatment-related irAEs, any fatal irAEs, and any irAEs leading to treatment interruption/dose reduction/discontinuation.

9.4.3. Pharmacokinetic Analysis

The PK parameters of C_{max}, t_{max}, C_{min}, AUC_{0-t}, and $AUC_{0-\tau}$ (INCB001158) for first 12 subjects enrolled in Phase 2 will be calculated from the blood plasma concentrations of INCB001158 using standard noncompartmental (model-independent) PK methods. Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin®. Nominal times will be used in all cases, except when the difference between the actual time and nominal time is greater than 15 minutes for samples collected up to 4 hours after administration and greater than 30 minutes for samples collected more than 4 hours after administration; in these cases, actual time will be used for PK analysis. See Appendix B for a detailed list and description of the PK parameters.

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

[redacted]

9.5. Interim Analyses

9.5.1. Interim Analysis for the BOIN Design

In Phase 1, the BOIN design will be used to determine the RP2D of INCB001158 in combination with each chemotherapy regimen. For the design parameters, let ϕ denote the target DLT rate, ϕ_1 denote the highest toxicity probability below the MTD so that dose escalation is required, and ϕ_2 denote the lowest toxicity probability deemed overly toxic so that dose de-escalation is required. We assume that $\phi_1 = 0.6\phi$ and $\phi_2 = 1.4\phi$. Also, to avoid assigning too many subjects to an overly toxic dose, we use the dose elimination rule when implementing the BOIN design. If $p_r(p_j > \phi \mid m_j, n_j) > 0.95$ and $n_j \geq 3$, then dose levels j and higher are eliminated from the study, and the study is terminated if the first dose level is eliminated, where p_j represents the toxicity rate, ϕ represents the target DLT rate, n_j represents the total subjects who have been treated, and m_j represents the subjects who have experienced toxicity at dose level j. Table 4 (in the bottom row) provides the elimination boundaries for the target DLT rate of 33%, respectively. For example, for the target DLT rate 33%, when the number of subjects treated at the current dose $n_j = 4$, we will eliminate that dose and higher doses if 3 or more subjects experience toxicity.

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

9.5.2. Interim Analysis for the Simon 2-Stage Design

In Phase 2, there will be a planned interim analysis for futility in each of the 6 expansion cohorts. The Simon 2-stage design will be applied for each expansion cohort independently. During Stage 1, n_1 evaluable subjects treated at the recommended dose and schedule will be enrolled (see Table 7), and if r_1 or fewer responses are observed, then the cohort will be discontinued. As discussed in Section 9.2.2, the Simon 2-stage designs for each tumor type have design parameters determined by historical response rates and will have different sample sizes and

different futility rules, depending on the historical response rate. Based on this early termination rule, the probabilities of early termination under the assumption of treatment interruption response rates (H_0) and desired response rates (H_A) are summarized in Table 24.

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

Cohort (Tumor Type)	p_0	p_1	Probability of Early Termination	
			Under H_0	Under H_A
A1 (MSS-CRC)	10%	30%	0.5995	0.1211
B1 (BTC)	20%	40%	0.5583	0.0834
B2 (OC)	15%	35%	0.5995	0.1211
C1 (GC)	15%	35%	0.5995	0.1211
C2 (EC)	15%	35%	0.5995	0.1211
C3 (OC)	15%	35%	0.5995	0.1211

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

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

The investigator will be responsible for:

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

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

10.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor before the end of the study. As part of his or her responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

10.2. Accountability, Handling, and Disposal of Study Drug

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

- Delivery of study drug to the study site.
- Inventory of study drug at the site.

- Subject use of the study drug including pill or unit counts from each supply dispensed.
- Return of study drug to the investigator or designee by subjects.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study subjects.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

10.3. Data Management

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

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

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

10.4. Data Privacy and Confidentiality of Study Records

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

Subject names will not be supplied to the sponsor or its designee, if applicable. Only the subject number and subject's initials (subject's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the subject's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor or its designee, IRB or IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.5. Financial Disclosure

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

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

10.6. Publication Policy

By signing the study Protocol, the investigator and his or her institution agree that the results of the study may be used by the sponsor, Incyte 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.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of

multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

10.7. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

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

Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulatio$_{n1}$
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

For Male Subjects Participating in the Study:

In addition to the aforementioned contraceptive methods, male subjects must also use a condom during intercourse from the time of first dose of study treatment and through at least 6 months + 93 days after last dose of study treatment. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

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

APPENDIX B. PHARMACOKINETIC ANALYTICAL PARAMETERS

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

APPENDIX C. DOSE MODIFICATIONS FOR MFOLFOX6

C.1. Criteria for Start of Cycle (Criteria for Administration on Day 1 of Each Cycle)

After confirmation that each subject meets criteria for the start of each cycle described in Table C-1, mFOLFOX6 will be administered. If any criteria are not met, administration of therapy will be postponed. From the second cycle onwards, study treatment will be discontinued if therapy has not been initiated by 14 days after the estimated Day 1.

Table C-1: Criteria for Administration of mFOLFOX6 on Day 1 of Each Cycle or Within a Cycle

Parameter		Criterion for Start
White blood cell count		$\geq 3 \times 10^9$/L
Neutrophil count		$\geq 1.5 \times 10^9$/L
Platelet count		$\geq 75 \times 10^9$/L
Infection		No fever (> 38.0°C or 100.4°F) suspect for infection
Nonhematologic toxicities	Diarrhea	≤ No water diarrhea
	Others	< Grade 2 (except for nausea, vomiting, anorexia, and fatigue)

If mFOLFOX6 is held for any of the reasons noted in Table C-1, INCB001158 may be continued at the discretion of the investigator with the approval of the medical monitor, and the subject will be evaluated at least weekly until the toxicity has resolved. The guidelines shown in Table C-2 and Table C-3 for hematologic toxicities will determine the dose selected for use in the new cycle, and the investigator will take tolerability of the most recent dose into account.

C.2. Dose Modifications for Hematologic Toxicities

Table C-2 provides guidance for dose reductions for the first appearance of the hematologic toxicities. Toxicities must be resolved to Grade 0 or 1 before resuming study treatment. When the dose of 5-fluoroucil (5FU) is reduced, the dose of leucovorin will remain the same.

Table C-2: Criteria for Dose Reductions for the First Appearance of Hematologic Toxicities

Criteria	INCB001158	Oxaliplatin	5FU Bolus	5FU Continuous
Grade 3 leukopenia or neutropenia	Resume at same dose.	20% dose reduction	Stop treatment	No dose reduction
Grade 4 leukopenia or neutropenia	Reduce 1 dose level.			
Grade 2 or 3 thrombocytopenia	Resume at same dose.			
Grade 4 thrombocytopenia	Reduce 1 dose level.			

Note: The dose of leucovorin remains the same.

Table C-3 provides guidance for dose reductions for the second appearance of the specified hematologic toxicities. Based on the most severe toxicity experienced since the last treatment, the following dose modifications will also be used for nonhematologic toxicities. When the dose of 5FU is reduced, the dose of leucovorin will remain the same. If oxaliplatin is discontinued for

peripheral neuropathy, then 5FU, leucovorin, and/or INCB001158 may be continued until additional discontinuation criteria are met.

Table C-3: Criteria for Dose Reductions for Recurrent Hematologic Toxicities

Criteria	INCB001158	Oxaliplatin	5FU Bolus	5FU Continuous
Grade 3 leukopenia or neutropenia	Resume at same dose.	20% dose reduction	N/A	No dose reduction
Grade 4 leukopenia or neutropenia	Reduce 1 dose level.			
Grade 2 or 3 thrombocytopenia	Resume at same dose.			
Grade 4 thrombocytopenia	Reduce 1 dose level.			

Note: The dose of leucovorin remains the same.

After a second dose reduction, if any hematologic toxicities reoccur (third occurrence) and are clearly associated with chemotherapy, then chemotherapy may be discontinued, and INCB001158 may be continued at the same dose at the discretion of the investigator and with the approval of the medical monitor.

C.3. Management Guidelines for Nonhematologic Toxicities

Table C-4 provides guidance for dose reductions for the appearance of nonhematologic toxicities. Toxicities must be resolved to Grade 0 or 1 before resuming study treatment. When the dose of 5FU is reduced, the dose of leucovorin will remain the same. Some adverse events (AEs) will overlap with potential immune-related adverse events (irAEs; eg, diarrhea and colitis/enteritis). In these cases, both the AE and irAE guidance should be reviewed to determine the most appropriate management of dose interruptions and dose reductions of study medications.

Table C-4: Criteria for Dose Reductions for Nonhematologic Toxicities

Criteria		INCB001158	Oxaliplatin	5FU Bolus	5FU Continuous
Allergic reaction to oxaliplatin		Discuss with medical monitor before restarting.	Stop treatment	No dose reduction	No dose reduction
AST/ALT	Grade 1 (< 3 × ULN)	Continue and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline.	No dose reduction	No dose reduction	No dose reduction
	Grade 2 (3 × to < 5 × ULN)	Hold LFTs twice weekly until resolves to ≤ Grade 1 or baseline. Resume at previous dose if recovers within 2 weeks. If AST/ALT does not resolve within 2 weeks, consider steroids. When recovered, reduced 1 dose level. If AST/ALT does not resolve within 6 weeks, discontinue or discuss with medical monitor.	No dose reduction	No dose reduction	No dose reduction
	Grade 3 or 4 (> 5× ULN)	Permanently discontinue.	20% dose reduction	Stop treatment	No dose reduction
Bilirubin	Grade 2 (> 1.5 × to 3 × ULN)	Hold and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline. Resume at previous dose if recovers within 2 weeks. If AST/ALT does not resolve within 2 weeks, consider steroids. When recovered, reduced 1 dose level. If AST/ALT does not resolve within 6 weeks, discontinue or discuss with medical monitor.	No dose reduction	No dose reduction	No dose reduction
	Grade 3 (> 3 × to 10 × ULN)	Permanently discontinue.	20% dose reduction	Stop treatment	No dose reduction
	Grade 4 (> 10 × ULN)	Permanently discontinue.	Stop treatment	Stop treatment	Stop treatment
Hy's Law[a]		Permanently discontinue.	Stop treatment	Stop treatment	Stop treatment

Table C-4: Criteria for Dose Reductions for Nonhematologic Toxicities (Continued)

Criteria		INCB001158	Oxaliplatin	5FU Bolus	5FU Continuous
Diarrhea	Grade 1	Continue, initiate supportive care.	No dose reduction	No dose reduction	No dose reduction
	Grade 2	Hold, initiate supportive care. Resume at previous dose if recovers to ≤ Grade 1 within 2 weeks. If diarrhea does not resolve within 2 weeks, consider steroids. When resolved to ≤ Grade 1 and steroids tapered, reduce 1 dose level. If AE does not resolve within 6 weeks, discontinue or discuss with medical monitor.	No dose reduction	No dose reduction	No dose reduction
	Grade 3 or 4	Hold, initiate supportive care and steroids. When resolved to ≤ Grade 1 and steroids tapered, reduce 1 dose level. If AE does not resolve within 6 weeks, discontinue or discuss with medical monitor.	20% dose reduction	Stop treatment	No dose reduction
Neurologic toxicities	Grade 2	Resume at same dose.	20% dose reduction	No dose reduction. Stop treatment for hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia or visual disturbances	
	Grade 3	Reduce 1 dose level.	Stop treatment		
Respiratory symptoms indicative of pulmonary fibrosis due to oxaliplatin		Discuss with medical monitor before restarting.	Stop treatment	No dose reduction	
Other nonhematologic toxicity	Grade 3	Reduce 1 dose level.	20% dose reduction	Stop treatment	No dose reduction
	Grade 4	Permanently discontinue unless discussed with medical monitor.	Stop treatment	Stop treatment	Stop treatment

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFT = liver chemistry test; ULN = upper limit of normal.

[a] Hy's law is defined as follows: 1) aminotransferase elevation (ALT or AST) > 3 × ULN; 2) total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP); 3) no other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, liver metastases, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.

APPENDIX D. DOSE MODIFICATIONS FOR GEMCITABINE/CISPLATIN

D.1. Criteria for Start of Cycle (Criteria for Administration on Day 1 of Each Cycle)

A cycle of therapy may begin on a scheduled Day 1 if the following conditions are met:

- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L.
- Platelet count is $\geq 100 \times 10^9$/L.
- Sensory neuropathy has improved to $\leq$ Grade 2 or returned to baseline.
- Any other AE that occurred has resolved to $\leq$ Grade 1 severity or returned to baseline.

The guidelines shown in Table D-1 will determine the dose for use in the new cycle, and the investigator will take tolerability of the most recent dose into account.

If new cycle starting requirements are not met, then regardless of dose modification, gemcitabine and/or cisplatin will be held, INCB001158 may be continued at the discretion of the investigator with the approval of the medical monitor, and the subject will be evaluated at least weekly until the toxicity has resolved.

From the second cycle onwards, study treatment will be discontinued if therapy has not been initiated within the 14 days after the scheduled Day 1.

D.2. Changes to Treatment Regimen During a Cycle for Hematologic Toxicities

Recommended dose interruptions and modifications of INCB001158, gemcitabine, and cisplatin on Days 1 and 8 of a cycle for hematologic toxicity are shown in Table D-1.

Table D-1: Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or Within a Cycle

Cycle Day	ANC ($\times 10^9$/L)		Platelets ($\times 10^9$/L)	Gemcitabine and Cisplatin
Day 1	< 1.5	OR	< 100	Delay dose until recovery
Day 8	0.5 to < 1.0	OR	50 to < 75	Dose as scheduled
	< 0.5	OR	< 50	Delay dose until recovery

D.2.1. Gemcitabine and Cisplatin Dose Modifications

Dose reductions or interruptions of gemcitabine and cisplatin on Days 1 and 8 are mandatory in the event of hematologic toxicities, as specified in Table D-1. However, other interruptions or reductions may occur for safety reasons at the discretion of the investigator. Gemcitabine and cisplatin treatment cycles may be delayed or the dose may be reduced for laboratory parameters or AEs that are judged to be related to gemcitabine or cisplatin. A maximum of 1 dose reduction is allowed for gemcitabine (25% reduction) and for cisplatin (20%; Table D-2). For dose reductions for safety, individual drug dose should follow prescribing information for dose modifications. Day 1 of each study cycle will correspond with the first day of chemotherapy administration. Thus, study cycles may become out-of-sync with the originally planned schedule. All assessments will shift to coincide with the revised treatment (cycle) schedule.

Table D-2: Gemcitabine and Cisplatin Dose Level Reductions

	Gemcitabine	Cisplatin
Full dose	100%	100%
First dose reduction	25% reduction	20% reduction
If additional dose reduction required	Discontinue	Discontinue

If neutropenia or thrombocytopenia reoccur (second occurrence) and are clearly associated with chemotherapy, then gemcitabine and cisplatin may be discontinued, and INCB001158 may be continued, at the discretion of the investigator and approval of the medical monitor.

D.3. Other Adverse Drug Reactions in Subjects With Gemcitabine and Cisplatin

Dose interruptions and modifications for gemcitabine and cisplatin for other adverse drug reactions are described in Table D-3.

Table D-3: Dose Modifications for Gemcitabine and Cisplatin Adverse Drug Reaction

	Gemcitabine	Cisplatin
Febrile neutropenia: Grade 3 or 4	Withhold until fever resolved and ANC $\geq 1.5 \times 10^9$/L; resume at lower dose level.	
Peripheral neuropathy: Grade 3 or 4	No dose reduction.	Withhold until improves to ≤ Grade 1; resume at next lower dose level.
Cutaneous toxicity: Grade 2 or 3	Reduce to lower dose level; discontinue treatment if toxicity persists.	Reduce to lower dose level; discontinue treatment if toxicity persists.
Gastrointestinal toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at lower dose level.	Withhold until improves to ≤ Grade 1; resume at lower dose level.

Note: If the subject meets more than 1 of the criteria listed, then dose modifications should always be based on the system showing the greatest degree of toxicity. Dose interruptions and modifications will be made at the discretion of the investigator.

If the toxicities listed in Table D-3 persist or reoccur despite 2 dose reductions and are clearly associated with chemotherapy, then gemcitabine cisplatin may be discontinued, and INCB001158 may be continued at the discretion of the investigator and approval of the medical monitor. If cisplatin must be discontinued for peripheral neuropathy, then gemcitabine and INCB001158 may be continued at the discretion of the investigator and approval of the medical monitor.

D.4. General Management Guidelines for Nonhematologic Toxicities

Table D-4 provides guidance for dose reductions for the appearance of nonhematologic toxicities. Toxicities must be resolved to Grade 0 or 1 before resuming study treatment. Of note, some AEs will overlap with potential irAEs (eg, diarrhea and colitis/enteritis). In these cases, both the AE and irAE guidance should be reviewed to determine the most appropriate management of dose interruptions and dose reductions of study medications.

Table D-4: Criteria for Dose Reductions for Nonhematologic Toxicities

Criteria		INCB001158	Gemcitabine	Cisplatin
AST/ALT	Grade 1 (< 3 × ULN)	Continue and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline.	No dose reduction	No dose reduction
	Grade 2 (3 × to < 5 × ULN)	Hold and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline. Resume at previous dose if recovers within 2 weeks. If AST/ALT does not resolve within 2 weeks, consider steroids. When recovered, restart at the same dose level. If AST/ALT does not resolve within 6 weeks, discontinue or discuss with medical monitor.	No dose reduction	Consider dose reduction
	Grade 3 or 4 (> 5 × ULN)	Permanently discontinue.	No dose reduction	Reduce at lower dose level
Bilirubin	Grade 2 (> 1.5 × to 3 × ULN)	Hold and monitor LFTs twice weekly until resolves to ≤ Grade 1 or baseline. Resume at previous dose if recovers within 2 weeks. If AST/ALT does not resolve within 2 weeks, consider steroids. When recovered, restart at the same dose level. If AST/ALT does not resolve within 6 weeks, discontinue or discuss with medical monitor.	No dose reduction	No dose reduction
	Grade 3 (> 3 × to 10 × ULN)	Permanently discontinue.	No dose reduction	Reduce at lower dose level
	Grade 4 (> 10 × ULN)	Permanently discontinue.	Stop treatment	Stop treatment
Hy's Law[a]		Permanently discontinue.	Stop treatment	Stop treatment

Table D-4: Criteria for Dose Reductions for Nonhematologic Toxicities (Continued)

Criteria		INCB001158	Gemcitabine	Cisplatin
Diarrhea	Grade 1	Continue, initiate supportive care.	No dose reduction	No dose reduction
	Grade 2	Hold, and initiate supportive care. Resume at previous dose if recovers to ≤ Grade 1 within 2 weeks. If diarrhea does not resolve within 2 weeks, consider steroids. When resolved to ≤ Grade 1 and steroids tapered, reduced 1 dose level. If AE does not resolve within 6 weeks, discontinue or discuss with medical monitor.	No dose reduction	No dose reduction
	Grade 3 or 4	Hold, and initiate supportive care and steroids. When resolved to ≤ Grade 1 and steroids tapered, reduce 1 dose level. If AE does not resolve within 6 weeks, discontinue or discuss with medical monitor.	Reduce at lower dose level	Reduce at lower dose level
Neurologic toxicities	Grade 2	Resume at same dose.	No dose reduction	No dose reduction
	Grade 3	Resume at same dose.	No dose reduction	Reduce at lower dose level
Other nonhematologic toxicity	Grade 3	Withhold until Grade 0-1. Reduce 1 dose level.	Reduce at lower dose level	Reduce at lower dose level
	Grade 4	Permanently discontinue unless discussed with medical monitor.	Reduce at lower dose level	Reduce at lower dose level

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFT = liver chemistry test; ULN = upper limit of normal.

[a] Hy's law is defined as follows: 1) aminotransferase elevation (ALT or AST) > 3 × ULN; 2) total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP); 3) no other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, liver metastases, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.

APPENDIX E. DOSE MODIFICATIONS FOR PACLITAXEL

E.1. Criteria for Start of Cycle (Criteria for Administration on Day 1 of Each Cycle)

After confirmation that each subject satisfies criteria for the start of each cycle described in Table E-1, paclitaxel will be administered. If any criteria are not met, then administration of therapy will be postponed. From the second cycle onwards, study treatment will be discontinued if administration of therapy has not been initiated by 14 days after the estimated Day 1.

Table E-1: Criteria for Administration of Paclitaxel on Day 1 of Each Cycle or Within a Cycle

Parameter		Criterion for Start
White blood cell count		$\geq 2.5 \times 10^9$/L
Neutrophil count		$\geq 1.0 \times 10^9$/L
Platelet count		$\geq 100 \times 10^9$/L
Renal function		> 30 mL/min AND < 10% change in glomerular filtration rate from previous cycle
Nonhematologic toxicities	Bilirubin	≤ 1.5 ULN

ULN = upper limit of normal.

If paclitaxel is held for any of the reasons noted in Table E-1, INCB001158 may be continued at the discretion of the investigator with the approval of the medical monitor, and the subject will be evaluated at least weekly until the toxicity has resolved. The guidelines shown in Table E-2 and Table E-3 will determine the dose selected for use in the new cycle, and the investigator will take tolerability of the most recent dose into account.

E.2. Paclitaxel Dose Modifications

Table E-2 provides guidance for dose reductions for the first appearance of the specified toxicities.

Table E-2: Criteria for Dose Reductions for Specified Toxicities

Hematologic toxicity	Dose modifications based on neutrophil and/or platelet count on day of treatment (Day 1)				
	ANC		**Platelet Count**	**Action**	**Dose Modification Following Recovery**
	$\geq 1.0 \times 10^9$/L	AND	$\geq 100 \times 10^9$/L	Dose as scheduled	Full dose
	$< 1.0 \times 10^9$/L	OR	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	No dose reduction
	$< 1.0 \times 10^9$/L	AND	$\leq 100 \times 10^9$/L	Delay 1 week until recovery	No dose reduction
NCI common toxicities	**Toxicity**	**Definition**		**Dose Modification**	
	Febrile neutropenia	ANC $< 0.5 \times 10^9$/L plus fever requiring IV antibiotics ± hospitalization		Reduce at 60 mg/m^2 for subsequent doses. Consider prophylactic ciprofloxacin.	
	Peripheral Neuropathy	Grade 2		Reduce to 70 mg/m^2.	
		≥ Grade 3		Discontinue if no recovery.	
	Other toxicities	Grade ≥ 2 toxicity (except alopecia)		Defer therapy for 1 week until resolved to ≤ Grade 1 and then resume at 70 mg/m^2. Discuss with medical monitor if > 1 week delay.	

ANC = absolute neutrophil count; IV = intravenous; NCI = National Cancer Institute.

Table E-3 provides guidance for dose reductions for hepatic impairment.

Table E-3: Management Guidelines for Hepatic Toxicity

Hepatic impairment	If hepatic function is impaired at baseline (bilirubin > 1.5 × ULN), then treatment should be started at reduced dose (70 mg/m^2). `For more severe impairment, treatment may proceed at reduced dose, at consultant's discretion, and with weekly monitoring of LFTs.

LFT = liver chemistry test; ULN = upper limit of normal.

APPENDIX F. CYP2C8 AND CYP3A4 INHIBITORS AND INDUCERS

Source: University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org. Accessed October 2016. Highlighted rows indicate recent additions to the lists at the time the database search was performed.

In Vivo CYP2C8 Inhibitors

Inhibitor	Therapeutic class	Inhibitor dosing (oral)	Substrate (oral)	Max AUC Ratio	PMID or NDA#	Published
Strong CYP2C8 INHIBITORS (yielding substrate AUCr ≥ 5-fold)						
gemfibrozil	Fibric Acid Derivatives	600 mg BID (5 days)	GSK1278863	**17.36**	27128455	2014 May
		600 mg BID (5 days)	dasabuvir	**11.30**	25646891	2015 Jul
		900 mg SD	repaglinide*	**8.26**	21778352	2011 Oct
clopidogrel	Anticoagulants and Antiplatelets	300 mg SD	repaglinide*	**5.08**	24971633	2014 Oct
MODERATE CYP2C8 INHIBITORS (yielding substrate AUCr ≥ 2-fold but < 5-fold)						
teriflunomide	Other Immunomodulators	14-70 mg QD (12 days)	repaglinide*	**2.42**	NDA # 202992	2012
deferasirox	Miscellaneous Agents	30 mg/kg QD (3 days)	repaglinide*	**2.27**	19940232	2010 Feb
WEAK INHIBITORS CYP2C8 (yielding substrate AUCr < 2-fold)						
telithromycin	Antibiotics	800 mg QD (3 days)	repaglinide*	**1.77**	16513447	2006
trimethoprim	Antibiotics	160 mg BID (3 days)	repaglinide*	**1.63**	15025742	2004 Apr
ketoconazole	Antifungals	200 mg BID (5 days)	rosiglitazone	**1.46**	15373932	2004 Oct
trimethoprim	Antibiotics	160 mg BID (4 days)	rosiglitazone	**1.37**	15371985	2004 Sep
cotrimoxazole (trimethoprim/sulfamethoxazole)	Antibiotics	160/800 mg BID (6 days)	dasabuvir	**1.33**	26895022	2016 Aug
lesinurad	Antigout and Uricosuric Agents	400 mg SD	repaglinide*	**1.31**	NDA # 207988	2015
rolapitant	Antiemetics	200 mg SD	repaglinide*	**1.27**	NDA # 206500	2015
fluvoxamine	Selective Serotonin Reuptake Inhibitors	50 mg BID (3.5 days)	rosiglitazone	**1.25**	16856883	2006 Dec

Note: *Repaglinide is also metabolized by CYP3A. It is a substrate of OATP1B1 as well. Hence, other metabolic pathways or transporters might also be involved.

In Vivo CYP2C8 Inducers

Inducer	Therapeutic class	Inducer dosing (oral)	Substrate (oral)	Max % ↓ AUC	% ↑ CL	PMID or NDA #	Published
Moderate Inducers (50% ≤ AUC ↓ < 80% or 2-fold ≤ CL↑ < 5-fold)							
rifampin	Antibiotics	600 mg QD (7 days)	repaglinide	**79.6**	Not Provided	15034704	2004 Apr
		600 mg QD (6 days)	rosiglitazone	**66.4**	203.6	15001966	2004 Mar
		600 mg QD (6 days)	pioglitazone	**53.8**	Not Provided	16390353	2006 Jan
carbamazepine	Anticovulsants	200 mg QD (3 days) then BID (21 days)	dasabuvir	**70.3**	Not Provided	NDA # 206619	2014
oral contraceptives	Oral Contraceptives	ethinyl estradiol/norgestimate 35/250 µg QD (21 days)	dasabuvir	**54.5**	Not Provided	NDA # 206619	2014
Weak Inducers (20% ≤ AUC ↓ < 50% or 1.25-fold ≤ CL↑ < 2-fold)							
flucloxacillin	Antibiotics	500 mg BD (7 days)	repaglinide	**46.8**	88.0	23807564	2013 Nov
lopinavir / RIT	Protease Inhibitors	800/200 mg QD (14 days)	dasabuvir	**46.0**	Not Provided	23807564	2016 Apr 15
darunavir / RIT	Protease Inhibitors	600 BID/100 QD (14 days)	dasabuvir	**29.6**	Not Provided	NDA # 206619	2014
atazanavir / RIT	Protease Inhibitors	300/100 QD (14 days)	dasabuvir	**22.4**	Not Provided	NDA # 206619	2014

For all the interactions, induction of minor pathways or transporters may also be involved.

Dasabuvir is approved by the FDA only for the use in combination with ombitasvir/paritaprevir/ritonavir (Viekira Pak), while it is approved by the EMA as a single drug (Exviera) for HCV treatment.

In Vivo CYP3A Inhibitors

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate AUCr > 5)						
VIEKIRA PAK[2]	Antivirals	See note[2]	tacrolimus[2]	55.76	25708713	2015 May
indinavir /RIT	Protease Inhibitors	800/100 mg BID (1 day)	alfentanil	36.5	19225389	2009 Mar
tipranavir/RIT	Protease Inhibitors	500/200 mg BID (2 days)	midazolam	26.91	20147896	2010 Jun
ritonavir	Protease Inhibitors	3 doses of 100 mg over 24 h	midazolam	26.41	20002087	2009 Dec
cobicistat (GS-9350)	None	200 mg QD (14 days)	midazolam	19.03	20043009	2010 Mar
indinavir	Protease Inhibitors	800 mg TID (7 days)	vardenafil	16.25	NDA # 021400	2003 Aug
ketoconazole	Antifungals	400 mg QD (4 days)	midazolam	15.9	8181191	1994 May
troleandomycin	Antibiotics	500 mg single dose	midazolam	14.8	15536460	2004 Dec
telaprevir	Antivirals	750 mg TID (16 days)	midazolam	13.5	22162542	2012 Oct
danoprevir / RIT	Antivirals	200/100 mg QD (14 days)	midazolam	13.42	23872824	2013 Nov
elvitegravir / RIT	Treatments of AIDS	150/100 mg QD (10 days)	midazolam	12.8	NDA # 203100	2012
saquinavir / RIT	Protease Inhibitors	1000/100 mg BID (14 days)	midazolam	12.48	19792991	2009 Oct
lopinavir / RIT	Protease Inhibitors	400/100 mg BID (2 days)	alfentanil	11.47	24067429	2013 Dec
itraconazole	Antifungals	200 mg QD (4 days)	midazolam	10.8	8181191	1994 May
voriconazole	Antifungals	200 mg BID (9 days)	midazolam	9.63	21937987	2011 Nov
mibefradil	Calcium Channel Blockers	100 mg single dose	midazolam	8.86	14517191	2003 Oct
LCL161	Cancer Treatments	600 mg single dose	midazolam	8.8	23585187	2013 Jun
clarithromycin	Antibiotics	500 mg BID (7 days)	midazolam	8.39	16432272	2006 Feb
posaconazole	Antifungals	400 mg BID (7 days)	midazolam	6.23	19302901	2009 Feb
telithromycin	Antibiotics	800 mg QD (6 days)	midazolam	6.2	NDA# 021144	2004
grapefruit juice DS[3]	Food Products	240 mL TID (2 days) and 90 min, 60 min, 30 min prior to midazolam	midazolam	5.95	12953340	2003 Aug
conivaptan	Diuretics	40 mg BID (5 days)	midazolam	5.76	NDA # 021697	2005
nefazodone	Antidepressants	100-200 mg BID (12 days)	midazolam	5.44	14551182	2003 Nov
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)	midazolam	5.29	21406602	2011 Jun
saquinavir	Protease Inhibitors	1200 mg TID (5 days)	midazolam	5.18	10430107	1999 Jul
idelalisib	Kinase Inhibitors	150 mg BID (8 days)	midazolam	5.15	25760671	2015 Aug
boceprevir	Antivirals	800 mg TID (6 days)	midazolam	5.05	NDA # 202258	2011

Moderate CYP3A Inhibitors (AUCr ≥ 2 and < 5)						
erythromycin	Antibiotics	1000 mg single dose	midazolam	**4.99**	25139487	2014 Dec
fluconazole	Antifungals	400 mg single dose	midazolam	**4.93**	16172184	2005 Oct
atazanavir / RIT	Protease Inhibitors	300/100 mg BID	maraviroc	**4.9**	18333863	2008 Apr
darunavir	Protease Inhibitors	1200 mg BID (14 days)	saquinavir	**4.9**	NDA # 021976	2006
diltiazem	Calcium Channel Blockers	60 mg TID (2 days)	midazolam	**4.06**	21209240	2011 Nov
darunavir / RIT	Protease Inhibitors	400/100 mg BID (8 days)	sildenafil	**4.0**	NDA # 021976	2006
dronedarone	Antiarrhythmics	400 mg BID (14 days)	simvastatin	**3.66**	NDA # 022425	2009
crizotinib	Kinase Inhibitors	250 mg BID (28 days)	midazolam	**3.65**	NDA # 202570	2011
atazanavir	Protease Inhibitors	400 mg QD (7 days)	maraviroc	**3.57**	18333863	2008 Apr
aprepitant	Antiemetics	80-125 mg QD (5 days)	midazolam	**3.29**	12891225	2003 Aug
casopitant	Antiemetics	120 mg QD (14 days)	midazolam	**3.13**	20840445	2010 Oct
amprenavir	Protease Inhibitors	1200 mg BID (10 days)	rifabutin	**2.93**	11158747	2001 Feb
faldaprevir	Antivirals	240 mg BID (14 days)	midazolam	**2.92**	25449227	2015 Apr
imatinib	Antineoplastic Agents	400 mg QD (7 days)	simvastatin	**2.92**	14612892	2003 Nov
verapamil	Calcium Channel Blockers	80 mg TID (2 days)	midazolam	**2.92**	8198928	1994 Mar
netupitant	Antiemetics	300 mg single dose	midazolam	**2.44**	23729226	2013 Oct
nilotinib	Kinase Inhibitors	400 mg BID (12 days)	midazolam	**2.4**	25418605	2015 Apr
grapefruit juice	Food Products	240 mL QD (4 days)	midazolam	**2.39**	10546919	1999 Oct
tofisopam	Benzodiazepines	100 mg TID (9 days)	midazolam	**2.36**	17989974	2008 Jan
cyclosporine	Immunosuppressants	Not provided (1-5 years)	midazolam	**2.21**	21753749	2011 Sep
ACT-178882	Renin Inhibitors	300 mg QD (14 days)	midazolam	**2.19**	22849770	2013 Dec
ciprofloxacin[4]	Antibiotics	500 mg single dose	sildenafil	**2.12**	16372380	2005 Dec
schisandra sphenanthera	Herbal Medications	3 capsules (= 11.25 mg deoxyschizandrin) BID (7 days)	midazolam	**2.05**	19552749	2009 May
isavuconazole	Antifungals	clinical dose (detail not provided)	midazolam	**2.03**	NDA # 207500	2015
cimetidine	H-2 Receptor Antagonists	200-400 mg QID (1.5 days)	midazolam	**2.02**	6152615	1984 Sep
FK1706	Central Nervous System Agents	60 mg QD (14 days)	midazolam	**2.01**	19889885	2010 Feb

Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2)						
tabimorelin	Hormone Replacement	2.86-3.21 mg QD (7 days)	midazolam	1.93	12610745	2003 Feb
ranolazine	Cardiovascular Drugs	1000 mg BID (7 days)	simvastatin	1.89	NDA # 021526	2006
amlodipine	Calcium Channel Blockers	10 mg QD (9 days)	simvastatin	1.8	23965645	2014 Apr
lomitapide	Other Antilipemics	60 mg QD (7 days)	simvastatin	1.77	24734312	2014 Mar
fosaprepitant (IV)	Antiemetics	150 mg single 30-min infusion	midazolam	1.76	21209230	2011 Dec
Seville orange juice	Food Products	240 mL single dose	felodipine	1.76	11180034	2001 Jan
amiodarone	Antiarrhythmics	400 mg QD (4 days)	simvastatin acid	1.76	17301736	2007 May
chlorzoxazone	Muscle Relaxants	250 mg single dose (part of a 6-drug cocktail)	midazolam	1.68	11736864	2001 Nov
M100240	Antihypertensive Agents	50 mg single dose	midazolam	1.66	15051745	2004 Apr
fluvoxamine	Antidepressants	50-00 mg BID (12 days)	midazolam	1.66	14551182	2003 Nov
ranitidine	H-2 Receptor Antagonists	150 mg BID (1.5 days)	midazolam	1.66	6135440	1983 Jun
fostamatinib[5]	Anti-inflammatory Drugs	100 mg BID (7 days)	simvastatin	1.64	26748647	2016 Mar
goldenseal	Herbal Medications	1,323 mg (= 24.1 mg isoquinoline alkaloids) TID (14 days)	midazolam	1.63	17495878	2008 Jan
clotrimazole	Antifungals	10 mg TID (5 days)	midazolam	1.61	20233179	2010 Feb
tacrolimus	Immunosuppressants	Not provided (1-5 years)	midazolam	1.61	21753749	2011 Sep
palbociclib	Kinase Inhibitors	125 mg QD (8 days)	midazolam	1.58	NDA # 207103	2015
cilostazol	Antiplatelets	100 mg BID (7 days)	lovastatin	1.56	10702889	1999
ticagrelor	Antiplatelets	180 mg bid (7 days)	simvastatin	1.56	NDA # 022433	2011
peppermint oil	Food Products	600 mg (= 300 uL peppermint oil) single dose	felodipine	1.55	12235445	2002 Sep
ivacaftor	Cystic fibrosis treatments	150 mg BID (6 days)	midazolam	1.54	25103957	2015 Jan
GSK2248761	Transcriptase Inhibitors	100 mg QD (12 days)	midazolam	1.54	22288567	2012 Aug
Guan Mai Ning	Herbal Medications	3 tablets TID (7 days)	simvastatin	1.51	25801058	2015 Sep
AZD2327	Depression Treatments	15 mg QD (7 days)	midazolam	1.49	26081137	2015 Nov
resveratrol	Food Products	500 mg QD (10 days)	carbamazepine	1.48	25624269	2015 May
roxithromycin	Antibiotics	300 mg QD (6 days)	midazolam	1.47	7995324	1994
suvorexant	Hypnotics - Sedatives	80 mg QD (14 days)	midazolam	1.47	NDA # 204569	2014
propiverine	Anticholinergics	15 mg BID (7 days)	midazolam	1.46	16183781	2005 Dec
isoniazid	Antibiotics	90 mg BID (4 days)	triazolam	1.46	6140941	1983 Dec
berberine	Herbal Medications	300 mg TID (14 days)	midazolam	1.45	21870106	2012 Feb
oral contraceptives	Oral contraceptives	OC with low doses of estrogen (< 35 ug ethinylestradiol) (> 3 months)	triazolam	1.44	6149030	1984 Nov
delavirdine	NNRTIs	400 mg TID (9 days)	indinavir	1.44	9665503	1998 Jul
daclatasvir	Antivirals	60 mg QD (7 days)	simeprevir	1.44	NDA # 205123	2013
simeprevir	Protease Inhibitors	150 mg QD (11 days)	midazolam	1.43	NDA # 205123	2013
atorvastatin	HMG CoA Reductase Inhibitors (Statins)	10-40 mg/day (chronic treatment)	midazolam IV	1.41	12911366	2003 Sep
tolvaptan	Vasopressin Antagonists	60 mg single dose	lovastatin	1.41	NDA # 022275	2009
almorexant	Hypnotics - Sedatives	200 mg QD (9 days)	midazolam	1.37	22990330	2013 Mar
GSK1292263	Other Antilipemics	300 mg BID (9 days)	simvastatin	1.36	23256625	2013 Jun
evacetrapid	CETP inhibitors	300 mg QD (15 days)	midazolam	1.35	26264702	2015 Dec
linagliptin	Dipeptidyl Peptidase 4 Inhibitors	10 mg QD (6 days)	simvastatin	1.34	20497745	2010 Jun
grazoprevir *(ingredient of Zepatier)*	Antivirals	200 mg QD (7 days)	midazolam	1.34	NDA # 208261	2016
lacidipine	Calcium Channel Blockers	4 mg QD (8 days)	simvastatin	1.33	11259986	2001 Feb
cranberry juice	Food Products	240 mL double strength juice, 1 glass q 15 min x 3	midazolam	1.33	19114462	2009 Mar
pazopanib	Kinase Inhibitors	800 mg QD (17 days)	midazolam	1.32	20881954	2010 Nov
everolimus	Immunosuppressants	10 mg QD (5 days)	midazolam	1.31	23426978	2013 Apr
blueberry juice	Food Products	two doses of 300 mL, separated by 16 hours	buspirone	1.31	22943633	2013 Apr
flibanserin	Central Nervous System Agents	50 mg BID (4 days)	simvastatin	1.31	NDA # 022526	2015
AMD070	Fusion Inhibitors	200 mg BID (8 days)	midazolam	1.29	18362694	2008 Apr

alprazolam	Benzodiazepines	1 mg TID (7 days)	buspirone	1.29	8300893	1993 Nov
Tong Xin Luo	Herbal Medications	4 capsules TID (7 days)	simvastatin	1.29	25801058	2015 Sep
bicalutamide	Antiandrogens	150 mg QD (>3 months)	midazolam	1.27	15509184	2004
sitaxentan	Endothelin Receptor Antagonists	100 mg QD (7 days)	sildenafil	1.27	20078609	2010 Jan
azithromycin	Antibiotics	500 mg QD (3 days)	midazolam	1.27	8720318	1996 Feb
ginkgo	Herbal Medications	120 mg TID (28 days)	midazolam	1.25	17050793	2006 Nov
teriflunomide	Other Immunomodulators	14-70 mg QD (14 days)	midazolam	1.25	NDA # 202992	2012

[1] To allow better comparability, DDI studies with the probe substrate midazolam were selected first.
When no study with midazolam was available, the AUCratio of another probe or sensitive substrate is presented.
[2] VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days. Tacrolimus is also a substrate of OATP1B1/1B3 that can be inhibited by Viekira Pak.
[3] 240 mL GFJ double-strength administered TID for 3 days
[4] Of note, co-administration of ciprofloxacin (750 mg BID for 7 days) did not affect plasma concentrations of ivacaftor, which is also a sensitive substrate for CYP3A (KALYDECO Prescribing Information).
[5] Fostamatinib also inhibits BCRP, and BCRP inhibition likely participates to the increase in exposure of simvastatin

In Vivo CYP3A Inducers

Inducers	Therapeutic class	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Dose (oral)	PMID or NDA #	Published
Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%))							
rifampin	Antibiotics	budesonide	99.7	36904.5	600 mg QD (7 days)	15726657	2005 Mar
mitotane	Other Antineoplastics	midazolam	94.5	Not Provided	maximum of 3.5 g TID (chronic therapy)	21220434	2011 Apr
avasimibe	Other Antilipemics	midazolam	93.5	Not Provided	750 mg/day (7 days)	12766253	2003 Sep
phenytoin	Anticonvulsants	nisoldipine	89.5	Not Provided	200-450 mg/day (chronic treatment)	8917062	1996 Nov
carbamazepine	Anticonvulsants	quetiapine	86.6	643.1	200 mg TID (26 days)	16390352	2006 Jan
enzalutamide	Antiandrogens	midazolam	85.9	Not Provided	160 mg QD (85±3 days)	NDA # 203415	2012
St John's Wort extract	Herbal Medications	midazolam	80.0	Not Provided	300 mg TID (14 days)	16341856	2006 Jan
rifabutin	Antibiotics	delavirdine	Not Provided	458.0	300 mg QD (14 days)	9224961	1997 Jun
phenobarbital	Anticonvulsants	verapamil	76.6	400.9	100 mg QD (21 days)	3392664	1988 Jul
Moderate Inducers (AUC decreased by 50-80% or CL increased by 2-5 fold (100-400%))							
ritonavir and St. Johns wort	None	midazolam	77.2	Not Provided	ritonavir: 300 mg BID and SJW: 300 mg TID (14 days)	19924124	2010 Feb
semagacestat	Alzheimer's Treatments	midazolam	76.4	324.6	140 mg QD (10 days)	22789530	2012 Oct
efavirenz	NNRTIs	alfentanil	76	369.4	600 mg QD (20 days)	22398970	2012 Apr
tipranavir and ritonavir	Protease Inhibitors	saquinavir	75.6	Not Provided	tipranavir: 500 mg and ritonavir: 200 mg BID (14 days)	18176328	2008 Apr
bosentan	Endothelin Receptor Antagonists	sildenafil	69.0	239.8	62.5-125 mg BID (8 weeks)	15963102	2005 Jul
genistein	Food Products	midazolam	13.7	136.9	1000 mg QD (14 days)	21943317	2012 Feb
thioridazine	Antipsychotics	quetiapine	68.7	104.5	100-300 mg QD (15 days)	22569350	2012 Jun
nafcillin	Antibiotics	nifedipine	62.6	145.1	500 mg 4 times daily (5 days)	12814453	2003 Jun
talviraline	NNRTIs	indinavir	61.7	181.2	500 mg TID (14 days)	10516944	1999 Oct
lopinavir	Protease Inhibitors	amprenavir	59.7	Not Provided	400 mg BID (4 weeks)	15060509	2004 Apr
modafinil	Psychostimulants	triazolam	57.6	35.7	200-400 mg QD (28 days)	11823757	2002 Jan
etravirine	NNRTIs	sildenafil	56.7	Not Provided	800 mg BID (13.5 days)	NDA# 022187	2008
lersivirine	NNRTIs	midazolam	51.4	105.5	1000 mg BID (14 days)	22527351	2012 Nov

Weak Inducers (AUC decreased by 20-50% or CL increased by 20-100% (less than 2 fold))							
eslicarbazepine	Anticonvulsants	simvastatin	49.4	98.4	800 mg QD (14 days)	23726291	2013 Sep
telaprevir	Antivirals	darunavir	48.4	Not Provided	1125 mg BID (4 days)	NDA# 201917	2011
garlic	Food Products	saquinavir	44.7	Not Provided	caplet of GarliPure BID (20 days)	11740713	2002 Jan
bexarotene	Other Antineoplastics	atorvastatin	45.3	Not Provided	400 mg/m2 QD (at least two 4-week cycles)	22057855	2012 Feb
artesunate and mefloquine	Antimalarials	lopinavir	43.1	75.4	4 mg/kg QD artesunate on Days 1-3 + 750 mg mefloquine on Day 1 and 500 m	26452725	2015
amprenavir (fosamprenavir)	Protease Inhibitors	lopinavir	43.0	Not Provided	700 mg BID (2-4 weeks)	15668539	2005 Jan
raltegravir	HIV-Integrase Strand Transfer Inhibitors	darunavir	42.0	Not Provided	400 mg BID	21958880	2012 Feb
lesinurad	Antigout and Uricosuric Agents	amlodipine	41.9	72.5	400 mg QD (24 days)	NDA # 207988	2015
vemurafenib	Kinase Inhibitors	midazolam	39.4	Not Provided	960 mg BID (15 days)	NDA # 202429	2011
troglitazone	Thiazolidinediones	simvastatin	37.7	Not Provided	400 mg QD (24 days)	11361054	2001 May
sorafenib	Kinase Inhibitors	sirolimus	36.9	Not Provided	200 mg BID (11 days)	21045832	2010 Nov
rufinamide	Anticonvulsants	triazolam	36.7	53.4	400 mg BID (11.5 days)	NDA # 021911	2008
sirukumab***	Immunomodulators Biologics	midazolam	35.7	Not Provided	300 mg single dose subcutaneously	26054042	2015 Dec
pleconaril	Antivirals	midazolam	34.6	52.8	400 mg TID (6 days)	16467135	2006 May
ginseng	Herbal Medications	midazolam	34.2	50.7	500 mg BID (28 days)	21646440	2012 Jun
boceprevir	Antivirals	darunavir	34.2	41.0	800 mg every 8 hrs (6 days)	23155151	2013 Mar
sulfinpyrazone	Antigout and Uricosuric Agents	cyclosporine	33.9 (change in C_{avg})		200 mg/day	11124491	2000 Dec
ginkgo	Herbal Medications	midazolam	33.7	52.6	120 mg BID (28 days)	18205997	2008 Feb
vinblastine	Vinca Alkaloids	midazolam IV	33.2	48.8	not provided (4 cycles)	20959500	2010 Nov
nevirapine	NNRTIs	indinavir	32.5	Not Provided	200 mg QD (14 days), then BID (19 days)	10191212	1999 May
armodafinil (R-modafinil)	Psychostimulants	midazolam	32.2	54.7	100-250 mg/day (31 days)	18076219	2008
ticagrelor	Anticoagulants and Antiplatelets	midazolam	31.7	46.5	400 mg QD (6 days)	23870610	2013 Jul
LCL161	Cancer Treatments	midazolam	29.8	34.0	600 mg single dose	23585187	2013 Jun

vicriviroc and ritonavir	Treatments of AIDS	ethinyl estradiol	**29.4**	Not Provided	30 mg vicriviroc and 100 mg ritonavir QD (10 days)	22015327	2011 Oct
ritonavir	Protease Inhibitors	ethinyl estradiol	**29.2**	Not Provided	100 mg QD (10 days)	22015327	2011 Oct
prednisone	Corticosteroids	tacrolimus	**29.0**	Not Provided	1.5 mg/kg/day	15787787	2005 Apr
oxcarbazepine	Anticonvulsants	felodipine	**28.1**	Not Provided	450 mg BID (7 days)	8451779	1993 Feb
danshen	Herbal Medications	midazolam	**27.9**	**32.8**	4 g TID (14 days)	20565457	2010 Jun
clobazam	Benzodiazepines	midazolam	**27.7**	Not Provided	40 mg QD (15 days)	22422635	2012 Apr
echinacea	Herbal Medications	midazolam	**27.3**	**37.5**	500 mg TID (28 days)	20653355	2010 Aug
ticlopidine	Anticoagulants and Antiplatelets	alfentanil	**27.0**	**50.0**	250 mg BID (4 days)	23361846	2013 Mar
isavuconazole	Antifungals	lopinavir	**27.0**	Not Provided	not provided (clinical dose)	NDA # 207500	2015
brivaracetam	Anticonvulsants	ethinyl estradiol	**26.8**	**37.3**	200 mg BID (21 days)	24386664	2013 Dec
Stribild*	Treatments of AIDS	ethinyl estradiol	**26.2**	**31.3**	150 mg ELV + 150 mg COB + 200 mg EMT+ 300 mg TEN	NDA # 203100	2012
pioglitazone	Thiazolidinediones	midazolam	**26.0**	Not Provided	45 mg QD 7 days	Actos® Product Label	2004 Aug
VIEKIRA PAK**	Antivirals	darunavir	**25.7**	Not Provided	See note**	NDA # 206619	2014
dexamethasone	Corticosteroids	aprepitant	**25.0**	Not Provided	8 mg/day (5 days)	NDA # 021549	2003
terbinafine	Antifungals	midazolam	**24.5**	Not Provided	250 mg QD (4 days)	8527290	1995 Sep
quercetin	Food Products	midazolam	**23.6**	Not Provided	500 mg QD (13 days)	21680781	2012 Jun
glycyrrhizin	Herbal Medications	midazolam	**23.0**	Not Provided	150 mg BID (15 days)	20393696	2010 Aug
aprepitant	Neurokinin-1 Receptor Antagonists	midazolam IV	**22.1**	**28.5**	125/80 mg QD (3 days)	14973304	2004 Mar
pretomanib (PA-824)	Antibiotics	midazolam	**22.1**	**20.7**	400 mg QD (14 days)	23689718	2013 Aug
oritavancin	Antibiotics	midazolam	**18.7**	**23.9**	1200 mg IV single infusion	NDA # 206334	2014
AZD 7325	Anxiolytics	midazolam	**18.7**	**22.6**	10 mg QD (12 days)	22122233	2012 Jul
methylprednisolone	Corticosteroids	cyclosporine	**15.8**	**35.0**	16 mg/day (12 days) then 8 mg/day (6 months)	12164891	2002 Sep
topiramate	Anticonvulsants	ethinyl estradiol	**12.0**	**20.2**	50 mg/day (21 days)	12681003	2003 Apr

1- Ritonavir has dual effects of simultaneous CYP3A inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity.
2- All the substrates presented in the table are sensitive CYP3A substrates (see definition in FDA guidance) except verapamil, cyclosporine, ethinyl estradiol, and delavirdine.

* **Stribild** is a combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF
** VIEKIRA PAK = paritaprevir/ritonavir/ombitasvir 150/100/25 mg QD + dasabuvir 250 mg BID for 14 days
*** Sirukumab is not a CYP inducer per se. It reverses the IL-6 mediated suppression of CYP3A activity in patients with active rheumatoid arthritis

APPENDIX G. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	31 OCT 2017
Amendment (Version) 2:	27 SEP 2018
Amendment (Version) 3:	17 MAY 2019
Amendment (Version) 4:	09 DEC 2020

Amendment 4 (09 DEC 2020)

Overall Rationale for the Amendment: The primary purpose of this amendment is to provide guidance for the management of ongoing subjects, as enrollment is complete and sufficient data have been collected for primary and secondary endpoint analysis.

1. **Synopsis; Section 4.5, Overall Study Duration; Section 5.2.1.4, Instructions to Subjects for Handling Study Drug (INCB001158); Section 5.5.1, Withdrawal Criteria; Section 5.6, Concomitant Medications; Section 5.6.3, Prohibited Medications; Section 6, Study Assessments (Table 15: Schedule of Assessments for All Subjects [as of Protocol Amendment 4]); Section 6.2, Treatment, Section 6.4.1, Safety Follow-Up; Section 6.4.2, Disease Status Follow-Up; [redacted] Section 7.6, Safety Assessments; Section 7.6.5, Laboratory Assessments; Section 7.6.5.4, Pregnancy Testing; Section 7.7, Efficacy Assessments; Section 7.7.1.3, End-of-Treatment and Follow-Up Imaging; [redacted]; Section 8, Safety Monitoring and Reporting; Section 8.1.2, Reporting; Section 8.2, Laboratory Test Abnormalities; Section 8.3.2, Reporting; Section 8.5, Pregnancy**

   Description of change: Study assessments for all subjects remaining on study treatment have been limited to standard of care for the subject's condition. Safety and efficacy data will only be collected for SAEs, AESIs, and disease assessment before Week 96. [redacted]

   Rationale for change: To update the study assessments as enrollment is complete and all ongoing subjects have been on study for more than 6 months or have met the definition of EOS as defined in Section 4.5.

2. **Section 4.6, Study Termination; Section 10.1.1, Identification of the Coordinating Principal Investigator; Section 10.6, Publication Policy; Section 10.7, Study and Site Closure**

   Description of change: Included the process for identification of the coordinating principal investigator and for study and site closure. Clarified the policy for study publications.

   Rationale for change: To update applicable sections as per current protocol template.

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

Amendment 3 (17 MAY 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to change the study drug formulation.

1. **Sections 5.2.1, INCB001158; 5.3, Treatment Compliance**

   Description of change: Replaced INCB001158 capsule formulation and blister card packaging with INCB001158 tablet formulation and bottle packaging.

   Rationale for change: Introduction of the study drug formulation and associated packaging.

2. **Section 6, Study Assessments (Table 11: Schedule of Assessments for Subjects Treated With INCB001158 + mFOLFOX6 or INCB001158 + Paclitaxel)**

   Description of change: Clarified that some clinical assessments planned on Day 8 of the treatment cycle are only for subjects receiving paclitaxel.

   Rationale for change: Clarification.

3. **Section 7.7.1, Tumor Imaging and Assessment of Disease**

   Description of change: Clarified that the images from scans may be sent to a central reader for independent image analysis.

   Rationale for change: Clarification.

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

Amendment 2 (27 SEP 2018)

Overall Rationale for the Amendment: The primary purpose of this amendment is to update the inclusion criteria for the microsatellite stable colorectal cancer (MSS-CRC) expansion cohort.

1. **Synopsis; Section 1.1.4, Overview of FOLFOX in Colorectal Cancer; Section 3.1, Subject Inclusion Criteria (Inclusion Criterion #12)**

   Description of change: Inclusion Criterion #12 was revised to indicate that subjects must have received 1 or 2 prior chemotherapy regimens for locally advanced/metastatic CRC.

   Rationale for change: To include subjects with 2 prior chemotherapy treatment lines.

2. **Synopsis; Section 3.1, Inclusion Criteria (Inclusion Criterion #16)**

   Description of change: Inclusion Criterion #16 was revised to indicate that subjects must have received 1 or 2 prior chemotherapy regimens for locally advanced/metastatic endometrial cancer.

   Rationale for change: To include subjects with 2 prior chemotherapy treatment lines.

3. **Section 6, Study Assessments (Table 11, Schedule of Assessments for Subjects Treated With INCB001158 + mFOLFOX6 or INCB001158 + Paclitaxel; Table 12, Schedule of Laboratory Assessments for Subjects Treated With INCB001158 + mFOLFOX6 or INCB001158 + Paclitaxel)**

   Description of change: Clarified that clinical and laboratory assessments planned on Day 8 of Cycle 2 and beyond are only for subjects who receive paclitaxel.

   Rationale for change: Clarification.

4. **Section 6, Study Assessments (Table 13, Schedule of Assessments for Subjects Treated With INCB001158 + Gemcitabine/Cisplatin; Table 14, Schedule of Laboratory Assessments for Subjects Treated With INCB001158 + Gemcitabine/Cisplatin)**

   Description of change: Clarified that administrative, clinical, and laboratory assessments planned on Day 15 of Cycle 2 and beyond are not performed.

   Rationale for change: Clarification.

5. **Section 6, Study Assessments (Tables 15, Laboratory Tests: Required Analytes)**

   Description of change: Clarified that amylase, lipase, urea, and CO_2 are included in the chemistries.

   Rationale for change: Clarification.

6. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: Provided the contraception method required for male subjects.

   Rationale for change: Informational.

7. **Appendix C, Dose Modifications for mFOLFOX6; Appendix D, Dose Modifications for Gemcitabine/Cisplatin; Appendix E, Dose Modifications for Paclitaxel**

   Description of change: Clarified that when the chemotherapy agents are held, INCB001158 may be continued at the discretion of the investigator with the approval of the medical monitor.

   Rationale for change: Clarification.

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

Amendment 1 (31 OCT 2017)

Overall Rationale for the Amendment: The primary purpose of this amendment is to address changes requested by the Medicines & Healthcare products Regulatory Agency (MHRA) in the United Kingdom.

1. **Section 1.3.1, Risk from INCB001158**

   Description of change: A statement was added noting that investigators advise patients take measures to minimize exposure to sun/ultraviolet light for the duration of the study and for 2 weeks after the last dose of study drug.

   Rationale for change: Requested by MHRA.

2. **Section 1.3.2, Risks From mFOLFOX6; Section 1.3.3. Risks From Gemcitabine/Cisplatin; Section 1.3.4, Risks From Paclitaxel**

   Description of change: A statement was added noting that investigators should advise male patients to consider conservation of sperm before enrollment in the study.

   Rationale for change: Requested by MHRA in line with the SmPCs of the chemotherapy agents.

3. **Section 3.1, Subject Inclusion Criteria**

   Description of change: Inclusion criterion 5 was revised to indicate that contraception must continue until 6 months after the last dose of the last component of study treatment.

   Rationale for change: Requested by MHRA in line with the SmPCs of the chemotherapy agents.

4. **Section 6, Study Assessments (Tables 12 and 14, Schedule of Laboratory Assessments; Table 15, Local Laboratory Tests: Required Analytes); Section 7.6.5.4, Pregnancy Testing**

   Description of change: Revised to indicate that urine pregnancy testing occurs on Cycle 1 Day 1 and Day 1 of each subsequent cycle.

   Rationale for change: Requested by MHRA.

5. **Sections 5.6.2, Restricted Medications; 5.6.3. Prohibited Medications; Appendix F, CYP2C8 and CYP3A4 Inhibitors and Inducers**

   Description of change: A statement was added noting that drugs that inhibit CYP2C8 or CYP3A4 must be used with caution, and drugs that induce CYP2C8 or CYP3A4 are not recommended with paclitaxel.

   Rationale for change: Requested by MHRA in line with the paclitaxel SmPC.

6. **Sections 5.6.2, Restricted Medications**

   Description of change: A statement was added noting that caution be used with concomitant therapies that are nephrotoxic or ototoxic to avoid additive toxicity with cisplatin.

   Rationale for change: Requested by MHRA in line with the cisplatin SmPC.

7. **Section 5.6.3, Prohibited Medications**

   Description of change: A statement was added noting that live vaccines must also be avoided for 3 months after the last dose of any component of study therapy.

   Rationale for change: Requested by MHRA.

8. **Section 1.3.1.3, Alterations in Hemodynamic Status; Section 6, Study Assessments (Tables 11 and 13, Schedule of Assessments); Section 7.6.3, Vital Signs**

   Description of change: A statement was added noting that orthostatic blood pressure will be monitored.

   Rationale for change: Requested by MHRA.

9. **Section 7.6, Safety Assessments**

   Description of change: A statement was added to clarify that subject safety management guidelines within the prescribing information for the chemotherapy agents should be followed as appropriate.

   Rationale for change: To ensure that the recommended safety management guidelines for the chemotherapy SmPCs are being followed.

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

Signature Page for VV-CLIN-000593 v6.0

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