Official Title: **A Phase 1/2, Open-Label, Dose-Escalation/Dose-Expansion, Safety and Tolerability Study of INCB059872 in Subjects With Advanced Malignancies**

NCT Number: NCT02712905

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Clinical Study Protocol

INCB 59872-101

A Phase 1/2, Open-Label, Dose-Escalation/Dose-Expansion, Safety and Tolerability Study of INCB059872 in Subjects With Advanced Malignancies

Product:	**INCB059872**
IND Number:	[redacted]
EudraCT Number	**2017-001710-28**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**15 DEC 2015**
Amendment (Version) 1:	**19 JAN 2016**
Amendment (Version) 2:	**28 JUL 2016**
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Amendment (Version) 5:	**30 JUL 2018**
Amendment (Version) 6:	**19 APR 2019**
Amendment (Version) 7:	**13 JUN 2019**
Amendment (Version) 8:	**15 JUN 2020**

INVESTIGATOR'S AGREEMENT

I have read the INCB 59872-101 Protocol Amendment 8 (Version 8 dated 15 JUN 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: INCB059872 (Lysine Specific Demethylase 1 Inhibitor)	
Title of Study: A Phase 1/2, Open-Label, Dose-Escalation/Dose-Expansion, Safety and Tolerability Study of INCB059872 in Subjects With Advanced Malignancies	
Protocol Number: INCB 59872-101	**Study Phase:** 1/2
Indication: Advanced Malignancies	

Primary Objectives:

- **Part 1:** To evaluate the safety and tolerability and determine the recommended dose(s) of INCB059872 for further study in advanced malignancies.
- **Part 2:** To further evaluate the safety and tolerability of INCB059872 for further study in advanced malignancies.
- **Part 3:** To evaluate the safety and tolerability and determine the recommended dose of INCB059872 in combination with other therapies for further study in advanced malignancies.
- **Part 4:** To further evaluate the safety and tolerability of INCB059872 in combination with other therapies in advanced malignancies.

Secondary Objectives:

- **Parts 1 and 2:** To assess preliminary antitumor activity of INCB059872 as a monotherapy in subjects with advanced malignancies.
- **Parts 3 and 4:** To assess preliminary antitumor activity of INCB059872 in combination with other therapies in subjects with advanced malignancies.
- To evaluate the pharmacokinetics (PK) of INCB059872 and assess the effect of food (Treatment Group [TG] B1 only) on the PK of INCB059872.

[redacted]

Primary Endpoints:

- **Parts 1 and 2:** Safety and tolerability as assessed by monitoring frequency, duration, and severity of adverse events (AEs) through physical examinations, by evaluating changes in vital signs and electrocardiograms (ECGs), and through clinical laboratory blood and urine sample evaluations.
- **Parts 3 and 4:** Safety and tolerability as assessed by monitoring frequency, duration, and severity of AEs through physical examinations, by evaluating changes in vital signs and ECGs, and through clinical laboratory blood and urine sample evaluations in combinations therapies.

Secondary Endpoints:

- **Parts 1 and 2:** Tumor response rates in those subjects with measurable disease or spleen volume changes as determined by investigator assessment of response per disease-specific guidelines.
  - Solid tumors: Objective response rate (ORR), defined as the percentage of subjects having complete response (CR) or partial response (PR) will be determined by the investigator assessment of radiographic disease assessments per RECIST v1.1.
  - Acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS): ORR, defined as the proportion of subjects who achieve CR or complete remission with incomplete hematologic recovery (CRi) per the International Working Group Response Criteria for Acute Myeloid Leukemia or the International Working Group Response Criteria for MDS, as applicable.
  - MF: Change and percentage change in spleen volume reduction (SVR) as measured by magnetic resonance imaging (MRI; computed tomography [CT] scan in subjects who are not a candidate for MRI or when MRI is not readily available) at Week 12 when compared with baseline.
- **Parts 3 and 4:** Tumor response rates in those subjects with measurable disease as determined by investigator assessment of response per disease-specific guidelines.
  - Small cell lung cancer (SCLC): ORR, defined as the percentage of subjects having CR or PR will be determined by the investigator assessment of radiographic disease assessments per RECIST v1.1.
  - AML/MDS: ORR, defined as the proportion of subjects who achieve CR or CRi per the International Working Group Response Criteria for Acute Myeloid Leukemia or the International Working Group Response Criteria for MDS, as applicable.
- PK parameters of INCB059872 in plasma: C_{max}, T_{max}, C_{min}, $AUC_{0\text{-}t}$, $t_{½}$, and Cl/F.

[redacted]

Overall Study Design:

This is an open-label, dose-escalation/dose-expansion study of the lysine-specific demethylase 1 (LSD1) inhibitor INCB059872 as a monotherapy and combination therapy in subjects with advanced malignancies. Subjects will receive INCB059872 doses once every other day (QOD) on a 28-day continuous therapy schedule; if QOD is well-tolerated, the next dose may be administered at a different dosing regimen (ie, once daily [QD]) but will not exceed the 100% dose escalation for a total daily dose. The study will be conducted in 4 parts: Parts 1 and 2 will evaluate INCB059872 as monotherapy, with Part 1 for dose escalation and Part 2 for dose expansion, and Parts 3 and 4 will evaluate INCB059872 in combination with select therapies, with Part 3 for combination dose escalation and Part 4 for combination dose expansion. Part 1 (monotherapy dose escalation) will determine the starting dose(s) of INCB059872

for dose expansion, based on maximum tolerated dose (MTD). The recommended dose(s) will be taken forward into Part 2 (monotherapy dose expansion). It is important to note that there may be a different MTD in different treatment groups. The initiation of Part 2 will be based on further review of the ongoing clinical study and preclinical data of INCB059872 and information from literature. Part 3 (dose escalation of INCB059872 in combination therapy) will be initiated after the MTD in Part 1 is determined. Part 4 (dose expansion of INCB059872 in combination therapy) will explore the dose(s) confirmed in Part 3 and the dose(s) may be different based on combination therapy and/or tumor type.

Monotherapy Dose Escalation (Part 1)

Approximately 24 subjects will be enrolled into each dose-escalation treatment group.

Treatment Group A will enroll subjects with AML or MDS. The enrollment in TG B is prioritized for SCLC. Enrollment of subjects with other solid malignancies (eg, endocrine tumors) is allowed with the sponsor medical monitor approval.

Dose escalation for TG A and TG B in Part 1 will proceed independently, with each treatment group following a 3 + 3 design. The starting dose of INCB059872 for TG A and TG B will be 2 mg QOD. A minimum of 3 subjects will initially be enrolled in each treatment group in Part 1, and each subject will be observed for a dose-limiting toxicity (DLT) observation period of 1 cycle (28 days) before the next dose cohort begins enrollment. Subjects must have taken at least 75% of the cohort-specific dose (at least 11 doses for QOD schedule or at least 21 doses for QD schedule) in the first 28 days of study treatment or have had a DLT to be considered evaluable. Subjects who are not evaluable will be replaced. The dose will be escalated by up to 100% if none (0) of the first 3 evaluable subjects enrolled has a DLT. Dose escalation should proceed in smaller increments (ie, by no more than 50%) if a DLT is observed, or if 2 or more subjects at a given dose level experience Grade 2 or higher AEs (unless they are clearly and incontrovertibly due to an alternative cause).

If 1 of the first 3 evaluable subjects enrolled has a DLT, the cohort will be expanded to include 3 additional evaluable subjects, and if no DLT occurs in the additional 3 subjects, then the dose will be escalated by up to 100%. Otherwise, if 2 subjects in a cohort of 3 or 6 subjects experience DLTs, the MTD will be deemed to be exceeded. An interim lower dose level may be explored if the dose increment has been 100%. The MTD will be defined as one dose level below the dose level at which one-third or more subjects experience DLTs. Upon the aggregate review of overall safety, PK, [redacted] and efficacy, a recommended dose (per tumor type) will be determined to maximize the clinical benefit/risk margin.

Monotherapy Dose Expansion (Part 2)

Upon identification of the recommended dose(s), up to 4 expansion cohorts per tumor type of approximately 15 subjects each may begin enrollment to further determine safety, tolerability, efficacy, PK, [redacted] of the selected dose(s). Treatment Group A1 will enroll subjects with AML or MDS and subjects in this cohort will have an opportunity to switch their treatment to a combination dose that is tested and found safe. Only subjects who have stable disease or better response for ≥ 3 months on monotherapy will be allowed to do so. Treatment Group A2 will enroll subjects with primary myelofibrosis (PMF) or secondary MF (post–polycythemia vera myelofibrosis [PPV-MF] or post–essential thrombocythemia myelofibrosis [PET-MF]). Treatment Group B1 will enroll subjects with SCLC. Treatment Group B2 will enroll subjects with Ewing's sarcoma and poorly differentiated neuroendocrine tumors. The selected doses for each treatment group are as follows:

- TG A1 dose will be 4 mg QD based on the safety and tolerability assessment in TG A.
- TG A2, TG B1, and TG B2 doses will be 3 mg QOD based on the safety and tolerability assessment in TG B (Part 1).

A study of the effect of food on the PK of INCB059872 will be conducted in Part 2, TG B1 only.

Note: Based on emerging data, the sponsor may decide to enroll specific subtypes of AML in TG A1.

If ≥ 5 subjects in the first 15 subjects of any cohort cumulatively (or more than 33% of subjects in cohorts

larger than 15 subjects) experience DLTs during Cycle 1, then further enrollment to the cohort will be stopped, and a lower dose level may be explored.

Individual dose titration will be permitted according to Protocol-defined safety parameters. Subjects will continue to receive INCB059872 in 28-day cycles until a withdrawal criterion is met.

Combination Dose-Finding (Part 3)

Part 3 enrollment will be initiated after the MTD has been determined in Part 1 and will include dose-finding to evaluate safety and tolerability of the combinations. Enrollment of Part 3 will occur in parallel with Part 2. Dose-finding will use a 3 + 3 design to evaluate different doses of INCB059872 in combination with other therapies in the following treatment groups:

- Combination TG C: INCB059872 in combination with all-trans retinoic acid (ATRA) in subjects with relapsed/refractory AML. The starting dose for INCB059872 in this cohort will be 2 mg QD (2 dose levels below the recommended dose for monotherapy expansion in TG A1).
- Combination TG D: INCB059872 in combination with azacitidine in subjects with newly diagnosed, treatment-naive AML or MDS with at least 5% bone marrow blasts and IPSS-R intermediate or higher risk disease who are unfit to tolerate standard intensive chemotherapy at study entry and who are eligible to receive azacitidine as first-line therapy for the disease under study. The starting dose for INCB059872 in this cohort will be 2 mg QD (2 dose levels below the recommended dose for monotherapy expansion in TG A1).
- Combination TG E: INCB059872 in combination with nivolumab in subjects with advanced SCLC previously progressed on platinum-based treatment. The starting dose for INCB059872 in this cohort will be 3 mg QOD (the recommended dose for monotherapy expansion in TG B1).

The starting dose of INCB059872 in the combination treatment groups will be based upon the tolerability of INCB059872 monotherapy identified in Part 1 of this study. Doses of the combination agents will be selected from conventional dose regimens and will remain the same for all dose-finding and dose-expansion cohorts. INCB059872 doses will not exceed the monotherapy MTD identified in Part 1. A minimum of 3 subjects will initially be enrolled in each treatment group in Part 3, and each subject will be observed for a DLT observation period of 1 cycle (28 days) before the next dose cohort or expansion to Part 4 begins enrollment. Subjects must have taken at least 75% of the cohort-specific dose (at least 11 doses for QOD schedule or at least 21 doses for QD schedule) in the first 28 days of study treatment or have had a DLT to be considered evaluable. Subjects who are not evaluable will be replaced.

If tolerated, the combination treatment groups will escalate independently and in parallel until the MTD or optimal doses of the combinations are identified and will be followed by independent expansion cohorts at the selected dose(s). If the starting dose is not tolerated in any of the combination treatment groups, a lower dose of INCB059872 may be explored; otherwise, higher doses found to be safe and tolerable in Part 1 may be explored. The sponsor, in consultation with participating investigators, may elect to expand a dose cohort(s) deemed tolerable, to up to 12 subjects, in order to obtain supplemental PK, [redacted], and safety data.

Combination Dose Expansion (Part 4)

Upon identification of the recommended dose(s) for each treatment combination in Part 3, expansion cohorts of approximately 30 subjects in each treatment group may begin enrollment to further determine safety, tolerability, efficacy, PK, [redacted] of the selected dose(s).

- Combination TG C1: INCB059872 in combination with ATRA using the regimen identified in Part 3 in subjects with relapsed/refractory AML.
- Combination TG D1: INCB059872 in combination with azacitidine using the regimen identified in Part 3 in subjects with newly diagnosed, treatment-naive AML or MDS with at least 5% bone marrow blasts and IPSS-R intermediate or higher risk who are unfit to tolerate standard intensive chemotherapy at study entry and who are eligible to receive azacitidine as first-line therapy for the disease under study.

- Combination TG E1: INCB059872 in combination with nivolumab using the regimen identified in Part 3 in subjects with advanced SCLC who previously progressed on platinum based treatment.

In Part 4, a stopping rule for futility is planned for each combination dose expansion treatment group. The futility analyses for combination TGs will be conducted when 15 subjects for each disease type have been treated and evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. The futility analyses for TG D1 will be conducted when the first 15 subjects with AML or when the first 15 subjects with MDS have been treated.

Study Population:

Potential subjects include those with advanced or metastatic malignancies who are ineligible for all therapeutic options that are standard of care or known to confer clinical benefit, or who refuse these treatments.

Key Inclusion Criteria:

- Male or female subjects, age 18 years or older.
- Presence of measurable disease that has been confirmed by histology or cytology. Myelofibrosis subjects must have palpable spleen of ≥ 5 cm below the left subcostal margin on physical examination at the screening visit.
- The following malignancy types will be included in each of the treatment groups:

	Treatment Group	Malignancy Histology
Part 1 (Dose Escalation)	A	AML or MDS
	B	SCLC (other solid tumors, eg, endocrine tumors, are allowed with medical monitor approval)
Part 2 (Dose Expansion)	A1	Relapsed/refractory AML or MDS
	A2	MF (PMF, PPV-MF, and PET-MF)
	B1	SCLC
	B2	Ewing's sarcoma and poorly differentiated neuroendocrine tumors
Parts 3 and 4 (Combination Dose Escalation/Expansion)	C/C1	Relapsed/refractory AML
	D/D1	Newly diagnosed, treatment-naive AML, or MDS who are unfit to tolerate standard intensive chemotherapy at study entry and who are eligible to receive azacitidine as first-line therapy for the disease under study.
	E/E1	SCLC previously progressed on platinum-based treatment

- Subjects must meet specific disease and treatment criteria as follows:
  - TG A/A1/A2, TG B/B1/B2, C/C1, and TG E/E1: The subject must not be a candidate for potentially curative therapy or standard-of-care approved therapy.
  - TG A2: The subjects must have confirmed diagnosis of PMF, PPV-MF, or PET-MF according to revised WHO 2016 criteria.
  - TG D/D1:
    Subjects with newly diagnosed, treatment-naive AML who are unfit to tolerate standard intensive chemotherapy at study entry based on at least 1 of the following criteria:
    - Age ≥ 75 years old.
    - History of congestive heart failure or documented ejection fraction ≤ 50%.
    - Pulmonary disease with diffusing capacity of the lungs for carbon monoxide ≤ 65% or FEVI ≤ 65%, or dyspnea at rest or requiring, oxygen.
    - Any other comorbidity that the physician judges to be incompatible with intensive chemotherapy.

OR
Subjects with newly diagnosed, treatment-naive MDS with at least 5% bone marrow blasts and IPSS-R intermediate or higher risk disease who are unfit to tolerate standard intensive chemotherapy at study entry and who are eligible to receive azacitidine as first-line therapy for the disease under study.
  - The following treatments for prior lower risk MDS are acceptable: Revlimid®, low-dose cytarabine, and growth factors.
- TG E/E1: The subjects in TG E must have previously received platinum-based therapy, but additional lines of therapies are allowed. The subjects in TG E1 must not have received more than 1 previous line of therapy for locally advanced or metastatic SCLC. The previous line of therapy must be a platinum-based therapy, and the subjects must have progressed on or after this treatment.

- Willingness to undergo a pretreatment bone marrow biopsy or aspirate (AML/MDS/MF) during screening (requirement may be waived with medical monitor approval). Subjects with solid malignancies must have baseline archival tumor specimen available: a tumor block or approximately 15 slides from biopsy or resection of primary tumor or metastasis that are < 2 years old (specimens > 2 years old may be accepted with medical monitor approval).
- ECOG performance status 0 to 2.
- Willingness to avoid pregnancy or fathering children based on the following criteria:
  - Woman of non-childbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy, ≥ 12 months of amenorrhea.)
  - Woman of childbearing potential who has a negative serum pregnancy test at screening and before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subjects and their understanding confirmed.
  - Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subjects and their understanding confirmed.

Key Exclusion Criteria:

- Receipt of anticancer medications, anticancer therapies, or investigational drugs within the following interval before the first administration of study drug (requirement may be waived with medical monitor approval):
  - < 5 half-lives or 14 days, whichever is longer, for any investigational agent
  - < 5 half-lives for all other anticancer medications
  - < 6 weeks for mitomycin-C or nitrosoureas
- Any unresolved toxicity ≥ Grade 2 from previous anticancer therapy except for stable chronic toxicities (≤ Grade 2) not expected to resolve.
- All treatment groups: prior receipt of an LSD1 inhibitor therapy. Parts 3 and 4 TG E/E1: prior receipt of anti–programmed cell death-1, anti–programmed death ligand 1, or anti–PD-L2 antibody.
- Any of the following laboratory results at screening without transfusions and hematopoietic growth factor support in solid tumors (no lower limits in AML and MDS, or in MF with medical monitor approval):

Laboratory Parameter	Value
Absolute neutrophil count ($\times 10^9$/L)	< 1.5
Hemoglobin (g/dL)	< 9.0
Platelet count ($\times 10^9$/L)	< 100

- Laboratory and medical history parameters outside Protocol-defined range unless associated with primary malignancy or metastatic disease and with medical monitor approval:
  - Total bilirubin > 1.5 × institutional upper limit of normal (ULN) if no liver metastases or > 3 × ULN in the presence of liver metastases or presence of documented Gilbert syndrome (unconjugated hyperbilirubinemia).
  - Aspartate aminotransferase or alanine aminotransferase > 2.0 × institutional ULN.
  - Creatinine clearance < 60 mL/min based on the institutional formula.
- History or evidence of bleeding disorder requiring treatment.
- History or presence of an abnormal ECG that in the investigator's opinion is clinically meaningful. A screening QTc interval > 470 milliseconds, as corrected by Fridericia, is excluded. For subjects with an intraventricular conduction delay (QRS interval 120 milliseconds), the JTc interval may be used in place of the QTc with sponsor approval. Subjects with left bundle branch block are excluded.
- Prior radiotherapy within 2 weeks of study treatment. Subjects must have recovered from all radiation-related toxicities, including radiation pneumonitis, and not require corticosteroids. Evidence of fibrosis within a radiation field from prior radiotherapy is permitted with medical monitor approval. A 1-week washout period is permitted for palliative radiation to non–central nervous system (CNS) disease with medical monitor approval.
- Unless approved by the medical monitor, allogeneic hematopoietic stem cell transplant within 6 months before treatment, or active graft-versus-host-disease following allogeneic transplant, or receipt of immunosuppressive therapy following allogeneic transplant within 2 weeks of Cycle 1 Day 1 (prednisone ≤ 10 mg/day is allowed).
- Unless approved by the medical monitor, autologous hematopoietic stem cell transplant within 3 months before treatment.
- History of human immunodeficiency virus infection.
- Untreated brain or CNS metastases or brain/CNS metastases that have progressed (eg, evidence of new or enlarging brain metastasis or new neurological symptoms attributable to brain/CNS metastases). Subjects with previously treated and clinically stable brain/CNS metastases and who are off all corticosteroids for ≥ 4 weeks are eligible.
- History of clinically significant or uncontrolled cardiac disease, including recent history (within 6 months) of unstable angina, acute myocardial infarction, New York Heart Association Class III or IV congestive heart failure, or arrhythmia requiring therapy.
- Pregnant or nursing women or subjects expecting to conceive or father children within the projected duration of the study, starting with the screening visit through completion of safety follow-up visit.
- Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
- Chronic or current active infectious disease requiring systemic antibiotics or antifungal or antiviral treatment, unless approved by sponsor medical monitor.
- Current use of prohibited medications.
- Inability or unlikeliness to comply with the dose schedule and study evaluations, in the opinion of the investigator.
- Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
- Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
- Inability to comprehend or unwilling to sign the informed consent form (ICF).

- Inability to swallow and retain oral medication.
- Evidence of active hepatitis B virus or hepatitis C virus infection.
- TG E/E1: Active, known or suspected autoimmune disease. Subjects are permitted to enroll with vitiligo, diabetes mellitus, resolved childhood asthma/atopy, residual hypothyroidism due to an autoimmune immune condition only requiring thyroid hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.
- TG C/C1: known allergy or reaction to any component of ATRA.
- TG D/D1: known allergy or reaction to any component of azacitidine.
- TG E/E1: known allergy or reaction to any component of nivolumab.

INCB059872/Study Drug, Dosage, and Mode of Administration:

INCB059872 will be self-administered orally QOD or QD on a 28-day cycle. In each cycle of the QOD dosing schedule, subjects should receive 14 doses of INCB059872. In each cycle of the QD dosing schedule, subjects should receive 28 doses of INCB059872. Tablets will be available in 1 mg strength. The initial starting dose for Part 1 will be 2 mg QOD. The initial starting dose for other parts of the study will be based on the aggregate data review of Part 1.

For QOD administration, if a dose is missed by more than 24 hours, the subject should skip the dose and take the next scheduled dose at the usual time. For QD administration, if a dose is missed by more than 4 hours, the subject should skip the dose and take the next scheduled dose at the usual time. INCB059872 tablet should be taken on an empty stomach if possible (refrain from food consumption during the period 2 hours before and 1 hour after taking INCB059872). For subjects participating in the food-effect portion of the study in Part 2, TG B1, a high-fat, high-calorie meal will be consumed within 30 minutes before taking INCB059872 on Cycle 2 Day 1.

Alternative dosing regimens (ie, once daily) may be explored based on emerging PK/[redacted] and safety data.

Reference Therapy, Dosage, and Mode of Administration:

Conventional regimens of the standard of care combination agents or nivolumab will be used throughout Parts 3 and 4 of the study. Tretinoin capsules (ATRA) will be administered as an open-label commercial product at a starting dose of 45 mg/m^2 per day as 2 evenly divided doses.

Azacitidine will be administered as an open-label commercial product at a starting dose of 75 mg/m^2 subcutaneously or intravenously for 7 days during the first 9-day or less period (ie, a 2-day break allowed on weekend, if needed) of each 28-day treatment cycle.

Nivolumab will be administered at a dose of 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks.

Premedications should be administered per standard-of-care guidelines.

Study Schedule/Procedures:

Subjects will have regularly scheduled study visits at the clinical site as part of a 28-day cycle. Study visits are as follows:

- Screening: Day -28 through Day -1
- Cycle 1: Day 1, 4, 8, 11, 15, 22
- Subsequent cycles: Day 1 (± 2 days; note that Day 1 must be a day with INCB059872 treatment) and Day 15 (± 2 days)
- End of treatment: Subjects must be seen and have blood drawn 2 times per week for 2 weeks after last dose.
- Safety follow-up: 30 days (+ 5 days) after the EOT visit or last dose of study drug if EOT visit not performed (or until toxicities resolve, return to baseline, are deemed irreversible, or the subject receives another anticancer therapy, whichever is shorter).

- Follow-up for disease status (only for subjects who discontinue for reasons other than disease progression).

Laboratory tests for safety

Study visits will include sample collection for hematology, chemistry, coagulation, lipid panel, and urinalysis. Additionally, the screening visit will include serology and fertility/pregnancy testing.

Laboratory tests for PK/[redacted]

Pharmacokinetic [redacted] samples will be collected at planned visits and shipped to the sponsor or designee for analysis.

Clinical assessments

Adverse event assessments, vital signs, ECG, physical examination, ECOG performance status, and disease response assessments will be performed by the investigative site.

An objective assessment of disease status will be performed as screening, appropriate to the malignancy type (eg, CT or MRI, bone marrow biopsy/aspirate, peripheral blood, as applicable by tumor type).

Estimated Duration of Participation:

It is estimated that an individual subject will participate for approximately 6 months. Subjects will participate in the study undergoing visits during screening and treatment in consecutive 28-day cycles, as long as the subject is receiving benefit and has not met any criteria for study withdrawal. The subject must complete screening within 28 days before first dose; the follow-up period is approximately 1 month after the last dose of INCB059872.

Estimated Number of Subjects: Approximately 215 subjects will be enrolled in this study.

Principal Coordinating Investigator: Dr. Michael Savona, MD

Statistical Methods:

Sample size consideration: Parts 1 and 3 of the study will use a 3 + 3 dose-escalation design, and the sample size will depend on the frequency of DLTs and the number of dose-escalation cohorts before reaching the MTD. For Part 2, up to approximately 15 subjects will be enrolled for each expansion cohort. The evaluation of 15 subjects will provide a $\geq$ 90% chance of observing at least 1 toxicity with a true event rate of $\geq$ 15%. For Part 4, for each of the combination cohorts (TG C1, TG D1, and TG E1) up to approximately 30 subjects will be enrolled. The evaluation of 30 subjects will provide approximately 90% chance of observing at least 1 toxicity with a true event rate of $\geq$ 7%.

All statistical analyses are exploratory in nature; descriptive statistics (eg, mean, standard deviation, range) will be derived where appropriate. The clinical safety data (vital signs, ECGs, laboratory tests, and AEs) will be descriptively summarized.

Pharmacokinetic [redacted] data will be analyzed. For subjects with solid tumor, AML, and MDS, the proportion of subjects who meet the response criteria as appropriate for the tumor type will be summarized with descriptive statistics. [redacted] For MF subjects, changes and percentage changes of spleen volume from baseline to Week 12 [redacted] will be summarized descriptively.

In Part 4, a stopping rule for futility is planned for each combination dose expansion treatment group. The futility analyses for combination TGs will be conducted when 15 subjects for each disease type have been treated and evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. The futility analyses for TG D1 will be conducted when the first 15 subjects with AML or when the first 15 subjects with MDS have been treated and evaluated. Combination TG C1 will be terminated for futility if $\leq$ 1 of the 15 subjects responded (ie, CR, CRi, morphologic leukemia-free state [MLFS]) based on assessments provided by investigator. Combination TG D1 will terminate enrollment for subjects with AML if $\leq$ 2 of the first 15 AML subjects respond (ie, CR, CRi, or MLFS), or will terminate enrollment for subjects with MDS if $\leq$ 2 of the first 15 MDS subjects responded (ie, CR or Marrow CR), based on assessments provided by investigator.

Combination TG E1 will be terminated for futility if ≤ 1 of the 15 subjects responded (ie, CR or PR) based on assessments provided by investigator.

Data Monitoring Committee:

No independent Data Monitoring Committee is planned for this study. Decisions to continue the enrollment in subsequent dose level cohort, dose level to be tested, as well as number of subjects to be evaluated, will be made after the appropriate data are collected and reviewed by sponsor representatives (eg, medical monitor) and investigators or designees. The group of sponsor representatives and investigators or designees will convene regularly (eg, once weekly) or ad hoc for specific discussions. Meeting minutes will be documented.

An internal Data Safety Monitoring Board (iDSMB) will review safety data at regular intervals throughout the study. The frequency of meetings will be contingent upon enrollment and availability of safety data for analysis and review. Details regarding membership, roles, and responsibilities of the committee are specified in the iDSMB charter.

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LIST OF ABBREVIATIONS

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

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APL	acute promyelocytic leukemia
AST	aspartate aminotransferase
ATRA	all-trans retinoic acid
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete response
CRi	complete remission with incomplete hematologic recovery
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNMT1	DNA methyltransferase 1
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
ED_{50}	median effective dose
EOT	end of treatment
FAB	French-American-British
FAD	flavin adenine dinucleotide
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HDAC	histone deacetylase
hERG	human ether-à-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act of 1996
HNSTD	highest non–severely toxic dose
HR	hazard ratio
IC_{50}	half maximal inhibition

Abbreviation	Definition
ICF	informed consent form
ICH	International Conference on Harmonisation
iDSMB	internal data safety monitoring board
IEC	independent ethics committee
IN	Investigator Notification
IPSS-R	Revised International Prognostic Scoring System
IRB	institutional review board
IRT	Interactive Response Technology
IV	intravenous
L-DAC	low-dose cytarabine
LSC	leukemia stem cell
LSD1	lysine-specific demethylase 1
MAO	monoamine oxidase
MDS	myelodysplastic syndrome
MDS-EB	myelodysplastic syndrome with excess blasts
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MLFS	morphologic leukemia-free state
[redacted]	
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NSCLC	non–small cell lung cancer
ORR	objective response rate
PD	pharmacodynamic
PD-1	programmed cell death-1
PD-L1	programmed death ligand 1
PET-MF	post–essential thrombocythemia myelofibrosis
[redacted]	
PK	pharmacokinetic
PMF	primary myelofibrosis
PPV-MF	post–polycythemia vera myelofibrosis
PR	partial response
Pro-GRP	pro–gastrin-releasing peptide
Q2W	every 2 weeks
QD	once daily
QOD	every other day

Abbreviation	Definition
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SC	subcutaneous
SCLC	small cell lung cancer
STD_{10}	severely toxic dose in 10%
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TG	Treatment Group
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

INCB059872 is a covalent flavin adenine dinucleotide (FAD)-directed inhibitor of lysine-specific demethylase 1 (LSD1) that is proposed for the treatment of advance malignancies. LSD1 regulates gene expression epigenetically by removing methylation marks from lysine 4 or 9 of histone H3. Target genes of LSD1 are involved in may biological processes, including cell growth, survival, differentiation, and stem cell homeostasis. Studies have shown that deregulated LSD1 activity is associated with human diseases, including cancer, where overexpression of LSD1 is frequently associated with poor clinical outcomes. Refer to the Investigator's Brochure (IB) for additional background information on INCB059872.

1.1.1. Lysine Demethylase 1 Inhibitor in Oncology

Epigenetic modifications significantly contribute to the development of various cancers (Dawson and Kouzarides 2012). Analyses of cancer genomes have revealed that multiple epigenetic regulatory genes are often overexpressed or mutated in a variety of cancers (Shen and Laird 2013). One particular epigenetic enzyme that is associated with human cancer is LSD1, the first discovered histone demethylase and a key epigenetic regulator of chromatin architecture (Shi et al 2004). Methylated histone marks on H3K4 and H3K9 are coupled with transcriptional activation and repression, respectively. As part of the corepressor complex (eg, as corepressor of RE1 silencing transcription factor) (Stavropoulos et al 2006), LSD1 has been reported to demethylate H3K4 and represses transcription, whereas LSD1 in the nuclear hormone receptor complex (eg, androgen receptor) may demethylate H3K9 to activate gene expression (Metzger et al 2005). This suggests that the substrate specificity of LSD1 can be determined by associated factors, thereby regulating alternative gene expression in a context-dependent manner. In addition to histone proteins, LSD1 demethylates several nonhistone proteins critical in the regulation of cell growth, differentiation, and survival pathways. These include p53 (Huang et al 2007), E2F (Kontaki and Talianidis 2010), STAT3 (Yang et al 2010), Tat (Sakane et al 2011), and myosin phosphatase target subunit 1 (Cho et al 2011). These findings suggest the potential for additional oncogenic roles of LSD1 beyond its epigenetic role in regulating chromatin remodeling. LSD1 also associates with other epigenetic regulators, such as DNA methyltransferase 1 (DNMT1) (Wang et al 2009) and histone deacetylase (HDAC) (You et al 2001). These associations augment the activities of DNMT or HDACs. LSD1 inhibitors may therefore potentiate the effects of HDAC or DNMT inhibitors (Han et al 2013, Singh et al 2011).

LSD1 contributes to a variety of biological processes, including the regulation of cell proliferation, the epithelial-mesenchymal transition, cellular transformation of somatic cells, and self-renewal and differentiation, the latter impacting stem cell biology both in embryonic stem cells and in cancer stem cells (Chen et al 2012, Adamo et al 2011). These cancer stem cells may render cancer cells resistant to conventional therapies, such as chemotherapy or radiotherapy, and promote tumor recurrence after treatment (Beck and Blanpain 2013). In this regard, LSD1 functions in maintaining an undifferentiated tumor initiating or cancer stem cell phenotype in a spectrum of cancers (Wang et al 2011, Zhang et al 2013). Notably, acute myeloid

leukemia (AML) cells retain a less differentiated stem cell–like phenotype or leukemia stem cell (LSC) potential. Genome-wide gene expression analyses have revealed that LSD1 regulates a subset of genes involved in multiple oncogenic programs to maintain the LSC phenotype in AML, and inhibition of LSD1 has demonstrated therapeutic benefit in preclinical models of murine and human AML (Harris et al 2012, Schenk et al 2012). A variety of additional hematologic cancers also overexpress LSD1, including significant subsets of high-grade B-cell and T-cell non-Hodgkin's lymphomas and Hodgkin's lymphomas (Niebel et al 2014), although the therapeutic benefit of LSD1 inhibition in these cancers has not yet been evaluated.

In addition to hematologic malignancies, overexpression of LSD1 is frequently observed in many types of solid tumors, and its expression is associated with a more clinically aggressive phenotype and poor prognostic outcome. Cancers in which overexpression of LSD1 has been documented include bladder cancer (Hayami et al 2011), small cell lung cancer (SCLC) (Mohammad et al 2015), non-SCLC (Lv et al 2012), breast cancer (Lim et al 2010), ovarian cancer (Konovalov and Garcia-Bassets 2013), glioma (Sareddy et al 2013), colorectal cancer (Hayami et al 2011, Ding et al 2013), a variety of sarcomas (Bennani-Baiti et al 2012), neuroblastoma (Schulte et al 2009), prostate cancer (Suikki et al 2010), esophageal squamous cell cancer (Yu et al 2013), papillary thyroid cancer (Kong et al 2013), and Ewing sarcoma (Sankar et al 2014). In these studies, either genetic knockdown of LSD1 expression or treatment with small-molecule inhibitors of LSD1 resulted in decreased cancer cell proliferation and/or induction of apoptosis both *in vitro* and *in vivo*. These findings suggest a potential therapeutic benefit of LSD1 inhibitors in a broad range of cancers beyond AML.

1.2. Overview of INCB059872

INCB059872 is a cyclopropylamine derivative. Other cyclopropylamine analogs covalently modify the cofactor FAD to inhibit the enzymatic activity of LSD1 (Ueda et al 2009, Suzuki and Miyata 2011). INCB059872 potently inhibited the enzymatic activity of LSD1, with an average half maximal inhibition (IC_{50}) value of 18 ± 3 nM. INCB059872 was highly specific for LSD1, as it did not inhibit LSD2 at 5 μM, nor monoamine oxidase-A (MAO-A) and MOA-B at concentrations as high as 20 μM.

1.2.1. Pharmacology of INCB059872

In enzyme-based assays, INCB059872 potently inhibited LSD1, with IC_{50} values of 18 ± 3 (average ± SD), while INCB059872 did not inhibit LSD2 and MAO-A/B. Both biochemical and *in vitro* pharmacodynamic (PD) assays consistently demonstrated that INCB059872 was a FAD-directed inhibitor of LSD1. In cellular assays, INCB059872 inhibition resulted in the upregulated expression of the differentiation markers, CD86 and CD11b, in multiple AML cell lines and human primary AML cells across the different French-American-British (FAB) subtypes. Using the human acute monocytic leukemia cell line, THP-1, spiked into human whole blood to estimate potency in the presence of human serum proteins, INCB059872 induced CD86 protein, with a half maximal effective concentration (EC_{50}) value of 23 ± 8 nM. Human AML cell lines showed various degrees of sensitivity to INCB059872 in cell proliferation assays, with EC_{50} values ranging from 17 to 314 nM, and treated cells underwent G1 cell cycle arrest. The antitumor activity of INCB059872 was further evaluated in human primary AML cells *ex vivo*.

The proliferation of a number of SCLC cell lines was also inhibited by INCB059872, with IC_{50} values ranging from 47 to 377 nM. Nontumorigenic cells, by contrast, were significantly less sensitive to INCB059872, with IC_{50} values > 10 μM in interleukin-2–stimulated T cells from normal donors. INCB059872 also demonstrated no significant effects on cellular proliferation or survival in HEK293 human embryonic kidney cells at concentrations up to 20 μM. These data demonstrate that INCB059872 inhibits LSD1 activity *in vitro*, and that inhibition of LSD1 results in the growth arrest and differentiation of cancer cells compared to normal cells. *In vitro* PD assays for LSD1 inhibition in AML cells showed that induction of the CD86 myeloid differentiation marker by INCB059872 was sustained for 5 days after removal of INCB059872 in culture. These results confirm that INCB059872 is a covalent FAD-directed inhibitor in cells.

In vivo, oral administration of INCB059872 demonstrated PD activity and efficacy in several models of human and murine AML and in human SCLC xenograft models in mice. Tumor PD analyses conducted in both the Molm-13 human AML systemic xenograft model and the THP-1 human AML subcutaneous (SC) xenograft model demonstrated induction of CD86 and CD11b expression, consistent with *in vitro* data. In these models, the PD activity of INCB059872 was marginal at a dose of 0.1 mg/kg and maximal at doses ≥ 0.5 mg/kg, demonstrating an *in vivo* median effective dose (ED_{50}) for CD86 induction of approximately 0.3 mg/kg. In addition, tumor PD responses were sustained for over 48 to 72 hours after dosing, suggesting a possible irreversible inhibition of LSD1 by covalent modification of FAD. Consistent with *in vivo* PD studies, once daily (QD) doses of INCB059872 greater than the *in vivo* ED_{50} showed significant and comparable antitumor effects in human AML cell line xenograft models, while doses less than the *in vivo* ED_{50} exhibited either no efficacy or marginal tumor growth inhibition in these tumor xenograft models. Similar effects of QD dosing regimens on tumor growth inhibition were observed in human SCLC tumor xenograft models (NCI-H562 and NCI-H1417), with a marked reduction in plasma pro−gastrin-releasing peptide (Pro-GRP) levels in INCB059872-treated NCI-H1417 tumor-bearing mice relative to vehicle controls. Alternative oral dosing regimens of INCB059872, including every other day (QOD), generally were comparably efficacious as a QD dosing regimen in these AML and SCLC xenograft models, consistent with the prolonged PD effects associated with INCB059872.

In the MLL-AF9 murine leukemia engraftment model in C57BL/6mice, the median survival of leukemic animals was significantly prolonged in mice receiving doses greater than or equal to a pharmacodynamically active oral dose of INCB059872 over a 14-day dosing period. These survival effects of INCB059872 in the MLL-AF9 murine AML model were associated with an expansion of the percentage of normal bone marrow cells, a reduction in LSCs, a decrease in the number of AML blast cells, the induction of myeloid differentiation, and a normalization of hematologic parameters to those of nonleukemic mice.

INCB059872 was evaluated against a panel of targets to assess the potential for unintended pharmacological activity. There was no significant cross-reactivity against any of the 55 *in vitro* binding assays in which INCB059872 was tested. INCB059872 was evaluated in kinase profiling assays at concentrations up to 20 μM, and no inhibitory activity for any of the 56 kinases tested was noted. INCB059872 was evaluated against a panel of selected ion cardiac channels (L-type calcium, human ether-à-go-go-related gene [hERG] potassium, hKir2.1 potassium, hKvLQT1/hminK potassium, hKv4.3 potassium, hNav1.5 sodium) in an automatic parallel patch clamp system; none of these channels was inhibited by more than 25% at 30 μM.

INCB059872 was also evaluated in the Good Laboratory Practice (GLP) *in vitro* hERG channel assay. The IC_{50} for hERG inhibition was 149.3 μM, which is > 4000-fold higher than the anticipated steady-state free C_{max} in humans. Collectively, these *in vitro* and functional results support the conclusion that the risk of unintended pharmacological activity is expected to be low.

1.2.2. Nonclinical Drug Metabolism and Pharmacokinetics of INCB059872

The absorption, distribution, metabolism, and excretion of INCB059872, a covalent FAD-directed inhibitor for LSD1, have been characterized in rats, dogs, and monkeys. Following intravenous (IV) administration, the systemic clearance was low in monkeys and dogs (23% and 29% of hepatic blood flow, respectively) and moderate in rats (37% of hepatic blood flow). The clearance mechanisms of INCB059872 include both cytochrome P450 (CYP)-dependent metabolism and non−enzyme-dependent catabolism. The administered dose excreted in urine as intact INCB059872 varied from approximately 9.9% in rats to 7.8% in dogs and 3.5% in monkeys, indicating renal clearance as minor elimination pathways. INCB059872 exhibited a moderate steady-state volume of distribution in all 3 species (0.9-1.5 L/kg), suggesting moderate distribution. After oral administration, oral bioavailability was moderate in monkeys (37%) but high in rats (70%) and dogs (100%). The terminal elimination half-life was 1.0 hour in rats, 1.2 hours in dogs, and 3.3 hours in monkeys. Despite a short half-life, sustained pharmacological activity was observed *in vitro* and *in vivo*, presumably a result of irreversible or covalent inhibition of LSD1, ie, a pharmacokinetic (PK)-PD divergence is expected for this mode of inhibition by INCB059872. Based on allometric scaling, the terminal elimination half-life in human is projected to be approximately 3 hours, and the oral bioavailability is projected to be 70%. Significant antitumor effects were observed in mice when peak plasma concentration exceeded the EC_{50} in the whole blood assay with either QD or QOD dosing. Based on preclinical PK-PD relationship assessment, the projected clinical dose for efficacy in patients is 2 mg QOD, which is expected to provide plasma concentrations exceeding the EC_{50} of 0.023 μM (based on THP-1 spiked whole blood assay with CD86 induction) for 2 hours, the total steady-state plasma $AUC_{0\text{-}48}$ and C_{max} is estimated to be approximately 0.2 μM·h and 0.05 μM, respectively.

INCB059872 exhibits moderate *in vitro* permeability across Caco-2 monolayers (3.8×10^{-6} cm/sec) and high aqueous solubility (20 mg/mL). *In vitro* transport studies indicate that INCB059872 is a weak substrate of efflux transporter P-glycoprotein, but not of breast cancer resistance protein. INCB059872 has limited penetration across the rat blood-brain barrier, with a steady-state brain-to-plasma ratio of 0.1. *In vitro* human protein binding of INCB059872 was low (unbound fraction of 73.5%), similar to that in preclinical species.

INCB059872 did not inhibit hepatic uptake transporters (OATP1B1 and OATP1B3). While INCB059872 was a weak inhibitor of renal uptake transporters (OCT2, OAT1, and OAT3), no drug-drug interactions are expected based on the projected steady-state human plasma C_{max} value. Moreover, INCB059872 did not inhibit P-glycoprotein or breast cancer resistance protein efflux transporters. Reaction phenotyping using recombinant human CYPs indicated that INCB059872 was metabolized by CYP2D6 and CYP3A4, and therefore it is possible that the PK of INCB059872 will be affected by coadministration of potent CYP2D6 inhibitors or CYP3A4 inhibitors/inducers. INCB059872 is not an inhibitor of the 6 CYPs evaluated, and therefore no drug-drug interaction is expected based on INCB059872 CYP inhibitory activities at pharmacologically relevant exposures of INCB059872. The metabolism profile of INCB059872

in rat, dog, monkey, and human *in vitro* liver preparations was qualitatively similar, with M1 (INCB061984) generated at levels > 10% of INCB059872 across all species. However, M1 was also generated in buffer or buffer fortified with rat bile, bilirubin, and FAD, indicating that nonenzymatic mechanisms are also involved in the formation of M1. There was no evidence of any human-specific metabolites. *In vivo*, parent INCB059872 was the most abundant component in rat and dog plasma, and M1 (INCB061984) was identified in rat plasma (approximately 4% of INCB059872) and dog plasma (approximately 40% of INCB059872).

1.3. Overview of Conventional Care Agents

1.3.1. All-Trans Retinoic Acid

All-trans retinoic acid (ATRA) is the acid form of vitamin A. It induces cell differentiation and decreases proliferation of acute promyelocytic leukemia (APL) cells by interrupting oncogenic transcriptional activities of retinoic acid receptor-alpha. It is currently indicated for use in patients with acute APL (Vesanoid PI 2010). Monotherapy of ATRA is associated with high complete remission rate, ranging from 70% to 85% (Huang et al 1988, Tallman et al 1997, Tallman et al 2002).

The intended use of ATRA in the proposed study is to assess safety and preliminary clinical benefit of the combination therapy with INCB059872. ATRA-based therapies have shown utility in clinical studies (Hoffman et al 2012). However, ATRA-based therapies have not been effective in non-APL AML, but the combination of ATRA and tranylcypromine (a nonspecific LSD1 inhibitor) unlocked the ATRA-driven therapeutic response and diminished the engraftment of primary human non-APL AML (Schenk et al 2012). Synergistic inhibition of leukemia cell viability was observed when ATRA was combined with INCB059872 in preclinical study. ATRA in combination with other agents, particularly those targeting epigenetics, has been shown to be potentially beneficial in myelodysplastic syndrome (MDS; Kuendgen et al 2005). ATRA metabolism is not affected by P450 enzyme, and its metabolic drug-drug interaction with INCB059872 is not anticipated.

1.3.2. Azacitidine

Azacitidine is a nucleoside metabolic inhibitor that is approved by the FDA and EMA for the treatment of patients with several different subtypes of MDS (Vidaza PI 2014). Azacitidine is thought to have 2 main mechanisms of antineoplastic action: cytotoxicity, resulting from incorporation into RNA and DNA, and DNA hypomethylation, restoring normal growth control and differentiation in hematopoietic cells (Kaminskas et al 2005). Several clinical studies have demonstrated the efficacy of azacitidine in MDS. In a Phase 2 clinical study evaluating azacitidine versus supportive care in high-risk MDS, Silverman et al (2002) reported a 60% overall response rate (including hematologic improvement) for azacitidine as compared with 5% receiving supportive care. Additionally, a Phase 3 study (Al-Ali et al 2012, Fenaux et al 2009) evaluating azacitidine versus conventional care in higher risk MDS revealed superior rates of hematologic response (29% vs 12%) and hematologic improvement (49% vs 29%) in the azacitidine group.

Azacitidine is recommended as a low-intensity induction therapy in AML, primarily in patients who are unfit for high- or intermediate-intensity regimens, especially in patients ≥ 60 years (NCCN 2017). In the AZA-AML-001 study (Dombret et al 2015), azacitidine (n = 241) was compared with conventional therapies (best supportive care, low-dose cytarabine [L-DAC], and standard induction therapy; n = 247) in patients age ≥ 65 years with newly diagnosed AML with > 30% bone marrow blasts. Median OS was improved (10.4 months vs 6.5 months, hazard ratio [HR] = 0.85, p = 0.10009) but did not reach statistical significance; mOS did reach statistical significance (12.1 months vs 6.9 months, HR = 0.76, p = 0.019) when the patients were censored at the start of subsequent AML therapy by prespecified sensitivity analysis. Also, patients with poor-risk cytogenetics (HR = 0.68) and with myelodysplasia-related changes (HR = 0.69) benefited significantly from azacitidine. Even though the study was not powered to compare azacitidine with individual conventional therapy, the OS of patients treated with azacitidine or L-DAC (n = 154 vs 158) did not differ significantly, and comparable survival rates were also observed comparing azacitidine with standard induction therapy (n = 43 vs 44), and azacitidine is superior to best supportive care by post hoc analysis. Azacitidine achieved a complete response (CR) of 19.5% versus 21.9% with conventional therapies, CR/complete remission with incomplete hematologic recovery (CRi) 27.8% versus 25.1%. The most common treatment-emergent adverse events (TEAEs) ≥ G3 occurring in ≥ 20% of patients in the azacitidine arm were febrile neutropenia, neutropenia, thrombocytopenia, pneumonia, and anemia. Although there has been limited investigation into the use of azacitidine in relapsed/refractory AML, Al-Ali et al (2012) reported a 10% overall response rate (including hematologic improvement) in subjects who were resistant to primary chemotherapy. Azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase. Cytochrome P450 enzyme induction or inhibition by azacitidine at clinically achievable plasma concentrations is unlikely, and metabolic drug-drug interaction between INCB059872 and azacitidine is not anticipated.

1.3.3. Overview of Nivolumab

Nivolumab is a fully human immunoglobulin G4 monoclonal antibody that selectively inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor to block the ligands programmed death ligand 1 (PD-L1) and PD-L2 from binding. The negative PD-1 receptor signaling that regulates T-cell activation and proliferation is therefore disrupted (Robert et al 2015). This releases PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. Nivolumab has demonstrated activity in early phase clinical studies, and Phase 3 studies (including CheckMate 331) are ongoing to evaluate the role of nivolumab in the management of relapsed SCLC. In the Phase 1/2 study CheckMate 032 (NCT01928394), multiple regimens of nivolumab were evaluated with (n = 61) or without (n = 98) ipilimumab in solid tumors, including SCLC. Durable responses were observed in both the nivolumab and the nivolumab + ipilimumab treatment arms in subjects with previously treated SCLC regardless of PD-L1 expression (Hellman et al 2017).

Nivolumab has been approved as monotherapy in the United States for the treatment of patients with unresectable or metastatic melanoma, metastatic non–small cell lung cancer (NSCLC), advanced renal cell carcinoma (RCC), recurrent or metastatic squamous cell carcinoma of the head and neck, and classical Hodgkin lymphoma. Nivolumab is also approved in combination with ipilimumab in patients with unresectable or metastatic melanoma (Opdivo PI 2017).

Nivolumab is approved in the European Union as monotherapy or in combination with ipilimumab for advanced (unresectable or metastatic) melanoma, as monotherapy for locally advanced or metastatic NSCLC after prior chemotherapy, for advanced RCC after prior therapy, and for Hodgkin lymphoma following autologous stem cell transplant and treatment with brentuximab vedotin (Opdivo SPC 2015).

1.4. Study Rationale

Cancer has several common characteristic that can be observed across numerous tumor types. One common characteristic is the uncontrolled growth and survival of cells and their ability to become invasive throughout the body. LSD1 contributes to tumor development by altering epigenetic marks on histones and nonhistone proteins. Accumulating data have validated that either genetic depletion or pharmacological inhibition of LSD1 normalizes oncogenic and cancer stem cell–like patterns of gene expression, thereby inducing differentiation programs, decreasing cell proliferation, and promoting apoptosis in cancer cells (Harris et al 2012, Schenk et al 2012). Therefore, LSD1 inhibitors have the potential to be effective treatments for human cancers with aberrant LSD1 activation.

1.5. Justification of Route, Dose Regimen, and Treatment Period

The starting dose of 2 mg INCB059872 administered QOD orally is proposed for this clinical study based on the assessment in GLP toxicology studies.

INCB059872 will be administered orally QOD or QD over a 28-day cycle. Part 1 will be a dose-escalating design in order to determine the recommended dose(s) of INCB059872 for dose-expansion (Part 2).

The proposed starting dose and schedule of INCB059872 for combination therapy is based on preclinical data and emerging clinical data from Part 1 of this study. To ensure safety of INCB059872 in combination with ATRA or azacitidine, the starting dose will be defined as 2 dose levels below the RP2D from Part 1 (monotherapy dose escalation). In Part 3, Treatment Group (TG) C, INCB059872 will be combined with ATRA (tretinoin) based on recent evidence to support synergism between ATRA and LSD1 inhibitors in AML (Schenk et al 2012). INCB059872 will be administered at a starting dose of 2 mg QD (2 dose levels below the RP2D) in combination with ATRA administered to subjects according to the commercial label (Vesanoid 2010), a starting dose of 45 mg/m^2 per day administered as 2 evenly divided doses. Treatment Group D will combine INCB059872 at a starting dose of 2 mg QD with azacitidine. The azacitidine regimen selected for use in this study (dose of 75 mg/m^2 SC or IV for 7 days during the first 9-day or less period [ie, a 2-day break allowed on weekend, if needed] of each 28-day treatment cycle) is appropriate to the patient population. The tolerability and activity of this regimen have been established (Lyons et al 2009, García-Delgado et al 2014) as an acceptable alternative to the recommended dosing schedule of Days 1 to 7 of each 28-day treatment cycle. If tolerated, TG C and TG D will escalate independently and in parallel until the maximum tolerated dose (MTD) or optimal dose(s) of the combination is identified. If the starting dose is not tolerated in any of the combination treatment groups, a lower dose of INCB059872 may be explored; otherwise, higher doses found to be safe and tolerable in Part 1 may be explored.

Treatment Group E will combine INCB059872 at the RP2D for solid tumors, 3 mg QOD, in combination with nivolumab administered at a dose of 3 mg/kg administered as an IV infusion over 60 minutes every 2 weeks. If the starting dose is not tolerated in any of the combination treatment groups, a lower dose of INCB059872 may be explored.

1.6. Potential Risks and Benefits of the Treatment Regimen

1.6.1. Potential Risks of INCB059872 Based on Preclinical Safety

The nonclinical safety program to support this IND was designed in accordance with ICH S9 for advanced cancer. In pivotal 1-month studies, INCB059872 was administered on a QOD regimen. The doses and dosing regimen for the pivotal GLP studies were selected based on the results of previous range-finding studies, where findings in the bone marrow (most prominent: abnormal megakaryocytes, decreased megakaryocytes) leading to marked thrombocytopenia resulted in subsequent internal and external hemorrhages in rats given ≥ 3 mg/kg (human equivalent dose 28.8 mg) QD and in dogs given ≥ 1 mg/kg (human equivalent dose 32.4 mg) QD. These observations suggested that QOD dosing may provide the best option for maximizing efficacy (which was similar after QD and QOD dosing regimens in nonclinical pharmacology studies) while minimizing toxicity (thrombocytopenia).

The primary INCB059872 toxicity findings included abnormal megakaryocyte morphology in bone marrow, thrombocytopenia, lower red blood parameters and higher reticulocytes, decreased mature granulocytes in the bone marrow and neutropenia, and increased monocyte count, and were attributed to the pharmacological activity of INCB059872. These findings were all partially or fully reversible after a 4-week recovery period. The toxicities produced by INCB059872 are similar to those described for a conditional LSD1 knockdown model in mice as described in literature (Sprüssel et al 2012), where LSD1 deficiency suppressed terminal granulopoiesis, erythropoiesis, and platelet production, with the exception of monopoiesis, which was promoted. Sprüssel et al (2012) also showed that peripheral blood granulocytopenia, monocytosis, anemia, and thrombocytopenia were reversible after restoration of LSD1 activity.

During the recovery period, a dose-dependent increase of platelet counts was observed. The maximum increase was about 3-fold compared to baseline values, and the peak time was approximately 14 days. The platelet counts returned to baseline values approximately 28 days after INCB059872 treatment cessation.

One dog administered 1 mg/kg QOD (the highest dose tested) in the 1-month study was euthanized; the cause of debilitation was an acute stomach ulcer. Although similar gastrointestinal findings were not observed in other animals, the relationship of this finding to INCB059872 could not be excluded.

There were no off-target toxicities identified in rats. INCB059872 was negative in the Ames mutagenicity assay.

The starting dose for this study was determined based on pharmacology-driven changes in bone marrow and peripheral blood (thrombocytopenia) in rats and dogs. In the 1-month GLP rat study, the severely toxic dose in 10% (STD_{10}) of rodents was above the highest tested dose of 2.1 mg/kg QOD (12.6 mg/m^2 per day). In the 1-month dog study, because a relationship of the acute stomach ulcer to INCB059872 in the animal euthanized in extremis at 1 mg/kg could not

be excluded, the highest non–severely toxic dose (HNSTD) was considered to be 0.4 mg/kg (8 mg/m^2 per day). The human equivalent dose associated with these doses are 20.2 mg (rat) and 13 mg (dog); applying a 10-fold safety factor for the rat and 6-fold safety factor in the dog results in doses of 2.02 mg and 2.17 mg, respectively. Thus, a starting dose of 2 mg INCB059872 QOD was selected for this study; it is projected to provide exposures above the whole blood EC_{50} for LSD1 inhibition for approximately 2 hours, and thus expected to be pharmacologically active. The total $AUC_{0\text{-}48}$ at this dose is projected to be 0.2 μM·h, which is approximately 2.5-fold lower (female dogs) and approximately 18-fold lower (male rats) than the unbound $AUC_{0\text{-}24}$ values for the HNSTD in dogs and STD_{10} in rats, as determined in the 1-month GLP studies.

Taking into consideration that INCB059872 is a covalent inhibitor of LSD1, C_{max}-based safety margins should also be considered: at 2 mg QOD, the human steady-state plasma C_{max} is projected to be approximately 0.05 μM (approximately 0.037 μM, unbound), which is approximately 5.8-fold lower (female dog) and approximately 30-fold lower (male rats) than the unbound C_{max} values for the HNSTD (dogs) and STD_{10} (rats), as determined in the 1-month GLP studies.

In summary, the starting dose of 2 mg INCB059872 administered QOD is considered to be safe for subjects based on the following:

- This dose was selected based on the overall toxicology assessment, including hematologic effects observed at the dog HNSTD and rat STD_{10}, and applying appropriate safety factors. These findings were not associated with evidence of extensive hemorrhage.
- There are adequate exposure-based safety margins projected for both the AUC and the C_{max} for the starting dose (2 mg).
- The main toxicities (eg, thrombocytopenia, neutropenia, and anemia) are manageable in the clinic.
- There is evidence for reversibility of all toxicities (eg, hematology and bone marrow effects).
- There is a plan for comprehensive evaluation of safety before each dose escalation.

1.6.2. Clinical Experience With INCB059872

Part 1 (dose escalation), which determines the starting dose(s) of INCB059872 for dose expansion and combination therapy based on the MTD has been open and enrolling since MAY 2016. Both QOD and QD schedules have been explored to collect safety, PK, and PD data to establish the optimal dose and schedule for patients with solid tumor and hematological malignancies. The safety was closely monitored by assessments as described in throughout this Protocol as well as the frequency, duration, and severity of adverse events (AEs). Patient status was discussed with the treating physicians during regular safety meetings.

In Part 1, the initial 2 mg QOD dose was well-tolerated by subjects in both treatment groups, TG A (AML/MDS) and TGB (solid tumors). As AML/MDS is a rapidly proliferating disease, it was decided in discussion with the participating investigators to use a daily dose (QD) schedule for TG A. A total of 17 subjects have been treated in 4 different cohorts (3 at 2 mg QOD, 6 at 2 mg QD, 5 at 3 mg QD, and 3 at 4 mg QD) in TG A. The treatment was generally

well-tolerated without any dose-limiting toxicities (DLTs). The monotherapy recommended Phase 2 dose for AML/MDS subjects was determined to be 4 mg QD.

In TG B, a total of 22 subjects have been treated in 6 different cohorts. The QOD schedules included 16 of those patients (3 at 2 mg QOD, 6 at 3 mg QOD, and 7 at 4 mg QOD) in 3 different cohorts. The QOD schedule was generally well-tolerated. There was 1 DLT of Grade 4 thrombocytopenia at 4 mg QOD. Further dose escalation was stopped, and the next lower dose cohort of 3 mg QOD was expanded to treat a total of 6 patients. No DLTs or Grade 3/4 thrombocytopenia were reported at 3 mg QOD, and this dose is the recommended Phase 2 dose for solid tumors. Dose escalation of the QD schedule in TG B has been halted due to 2 DLTs in the 3 mg QD cohort and 1 DLT in the 2 mg QD cohort; however, a lower dose of 1 mg QD is currently ongoing. Table 1 summarizes the number of subjects who enrolled in Study INCB 59872-101 by treatment cohort, as of the data cutoff date.

Table 1: Number of Subjects Who Enrolled in Study INCB 59872-101 (as of 10 JUL 2017)

Treatment	Number of Subjects
Total number of subjects exposed to INCB059872	39
TG A: AML	17
2 mg QOD	3
2 mg QD	6
3 mg QD	5
4 mg QD	3
TG B: SCLC (and other solid tumors with medical monitor approval)	22
2 mg QOD	3
3 mg QOD	6
3 mg QD	3
4 mg QOD	7
2 mg QD	1
1 mg QD	2

Preliminary unaudited data, as of 10 JUL 2017, are presented here for 39 subjects who have been treated with INCB059872 doses of 1 mg QD, 2 mg (QOD or QD), 3 mg (QOD or QD), and 4 mg (QOD or QD). Eight subjects were receiving treatment as of the data cutoff date. Of the 39 subjects, 12 subjects have received INCB059872 for > 20 days, 14 subjects have received INCB059872 for > 30 days, and 6 subjects have received INCB059872 for > 90 days.

Table 2 and Table 3 summarize TEAEs in descending order that occur in at least 3 subjects total for each treatment group. The most frequent TEAEs among all dose cohorts in TG A were fatigue and nausea (6 subjects each). The most frequent TEAEs among all dose cohorts in TG B were thrombocytopenia and dysgeusia (9 subjects each).

Based on preclinical data generated to date, there is reason to believe that subjects may develop some level of thrombocytopenia. As of the data cutoff date, 6 DLTs of ≥ Grade 3 thrombocytopenia or platelet count decrease have been reported in the 2 mg QD, 3 mg QD, and

4 mg QOD cohorts in TG B (1, 2, and 3 respectively). Treatment interruption occurred in the subjects with DLTs and resumed following recovery; 4 of these subjects resumed study treatment at a reduced dose (3 mg QOD).

Four treatment-emergent serious adverse events (SAEs) resulted in discontinuation of study treatment: thrombocytopenia, bile duct obstruction, epistaxis, and hypotension. With the exception of thrombocytopenia, none of these TEAEs leading to INCB59872 discontinuation were considered related to study treatment. Five treatment-emergent SAEs have resulted in death, none of which were considered related to study treatment by the investigators: leukocytosis, sepsis, pulmonary alveolar hemorrhage, respiratory failure, and gastrointestinal hemorrhage.

Table 2: Treatment Group A: Summary of Treatment-Emergent Adverse Events Occurring in at Least 3 Subjects in Decreasing Order of Frequency by Subject Total, Any Grade (Preliminary Data From Study INCB 59872-101)

MedDRA Preferred Term	2 mg QD	2 mg QOD	3 mg QD	4 mg QD	Total
Number of subjects enrolled as of the data cutoff date	6	3	5	3	17
Number of subjects who had at least 1 TEAE	6	3	5	3	17
Fatigue	0	3	2	1	6
Nausea	1	2	2	1	6
Decreased appetite	2	1	1	1	5
Febrile neutropenia	1	1	1	2	5
Anaemia	0	0	2	2	4
Dysgeusia	1	0	2	1	4
Hypophosphatemia	1	0	1	2	4
Vomiting	2	1	0	1	4
Cough	1	1	1	0	3
Diarrhoea	0	1	2	0	3
Hypotension	1	1	1	0	3
Platelet count decreased	0	0	1	2	3
Weight decreased	2	0	1	0	3

Table 3: Treatment Group B: Summary of Treatment-Emergent Adverse Events Occurring in at Least 3 Subjects in Decreasing Order of Frequency by Subject Total, Any Grade (Preliminary Data From Study INCB 59872-101)

MedDRA Preferred Term	1 mg QD[a]	2 mg QD	2 mg QOD	3 mg QD[b]	3 mg QOD	4 mg QOD	Total
Number of subjects enrolled as of the data cutoff date	2	1	3	3	6	7	21
Number of subjects who had at least 1 TEAE	1	1	3	3	6	7	20
Thrombocytopenia	0	1	0	2	2	4	9
Dysgeusia	0	0	3	2	1	3	9
Fatigue	0	0	2	2	1	3	8
Nausea	0	0	2	0	4	1	7
Constipation	0	0	0	1	3	1	5
Platelet count decreased	0	0	1	1	1	2	5
Diarrhoea	1	0	3	0	0	1	5
Decreased appetite	0	0	1	1	2	0	4
Neutropenia	0	0	0	2	0	2	4
Abdominal pain	0	0	1	0	2	0	3
Stomatitis	0	0	0	0	2	1	3
Vomiting	0	0	1	0	2	0	3
AST increased	0	0	0	1	1	1	3

[a] AE data not complete for this cohort.
[b] All subjects had a dose interruption and dose reduction to 3mg QOD in the first cycle.

1.6.3. Potential Risks of All-Trans Retinoic Acid

Boxed warnings for ATRA include retinoic acid–APL syndrome characterized by fever, dyspnea, acute respiratory distress, weight gain, radiographic pulmonary infiltrates, pleural and pericardial effusions, edema, and hepatic, renal, and multiorgan failure; rapidly evolving leukocytosis; and teratogenicity. Evaluation and management should be performed as described in the package insert (Vesanoid 2010).

Additional risks and precautions according to the package insert include headache, fever, dry skin, dry mucous membranes, bone pain, nausea and vomiting, rash, mouth sores, itching, sweating, eyesight changes, flu-like symptoms, coagulation disorder, infections, swelling of feet or ankles, bone/joint pain, and abdominal pain. A complete discussion of risks associated with ATRA can be found at http://dailymed.nlm.nih.gov/.

1.6.4. Potential Risks of Azacitidine

The primary DLT observed with azacitidine therapy is myelosuppression, typically manifesting as leukopenia, anemia, thrombocytopenia, and/or neutropenia. Hematologic toxicities are reversible and are managed through dose interruptions and/or reductions. Subjects will have blood counts monitored weekly during the first cycle of treatment and before starting each course of therapy thereafter, at a minimum. Azacitidine has also been associated with severe adverse reactions, including hepatic coma and renal failure. Subjects with significant baseline hepatic or renal impairment are excluded from this clinical study. Additional adverse reactions associated with the use of azacitidine (≥ 20%) include nausea, vomiting, constipation, diarrhea, fever, dyspnea, petechiae, and ecchymosis. A complete discussion of risks associated with azacitidine can be found at http://dailymed.nlm.nih.gov/.

1.6.5. Potential Risks Associated With Nivolumab

Due to the mechanism of action of nivolumab, immune-mediated adverse reactions have been seen when used as monotherapy and in combination with ipilimumab. Guidance is provided in the package insert for the management of immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated skin adverse reactions, and immune-mediated encephalitis. Infusion reactions are also possible following administration of nivolumab. The most common adverse reactions seen in ≥ 20% of patients receiving nivolumab monotherapy were fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenic conditions, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, and pyrexia. The most common adverse reactions seen in ≥ 20% of subjects receiving nivolumab in combination with ipilimumab were fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea (Opdivo PI 2017). Refer to the nivolumab prescribing information and EU summary of product characteristics for updated information regarding safety and risks.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

- **Part 1:** To evaluate the safety and tolerability and determine the recommended dose(s) of INCB059872 for further study in advanced malignancies.
- **Part 2:** To further evaluate the safety and tolerability of INCB059872 for further study in advanced malignancies.
- **Part 3:** To evaluate the safety and tolerability and determine the recommended dose of INCB059872 in combination with other therapies for further study in advanced malignancies.
- **Part 4:** To further evaluate the safety and tolerability of INCB059872 in combination with other therapies in advanced malignancies.

2.1.2. Secondary Objectives

- **Parts 1 and 2:** To assess preliminary antitumor activity of INCB059872 as a monotherapy in subjects with advanced malignancies.
- **Parts 3 and 4:** To assess preliminary antitumor activity of INCB059872 in combination with other therapies in subjects with advanced malignancies
- To evaluate the PK of INCB059872 and assess the effect of food (TG B1 only) on the PK of INCB059872.

[redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoints

- **Parts 1 and 2:** Safety and tolerability as assessed by monitoring frequency, duration, and severity of adverse events (AEs) through physical examinations, by evaluating changes in vital signs and electrocardiograms (ECGs), and through clinical laboratory blood and urine sample evaluations.
- **Parts 3 and 4:** Safety and tolerability as assessed by monitoring frequency, duration, and severity of AEs through physical examinations, by evaluating changes in vital signs and ECGs, and through clinical laboratory blood and urine sample evaluations in combinations therapies.

2.2.2. Secondary Endpoints

- **Parts 1 and 2:** Tumor response rates in those subjects with measurable disease or spleen volume changes as determined by investigator assessment of response per disease-specific guidelines.
  - Solid tumors: Objective response rate (ORR), defined as the percentage of subjects having complete response (CR) or partial response (PR) will be determined by the investigator assessment of radiographic disease assessments per RECIST v1.1.
  - Acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS): ORR, defined as the proportion of subjects who achieve CR or complete remission with incomplete hematologic recovery (CRi) per the International Working Group Response Criteria for Acute Myeloid Leukemia or the International Working Group Response Criteria for MDS, as applicable.
  - MF: Change and percentage change in spleen volume reduction (SVR) as measured by magnetic resonance imaging (MRI; computed tomography [CT] scan in subjects who are not a candidate for MRI or when MRI is not readily available) at Week 12 when compared with baseline.
- **Parts 3 and 4:** Tumor response rates in those subjects with measurable disease as determined by investigator assessment of response per disease-specific guidelines.
  - Small cell lung cancer (SCLC): ORR, defined as the percentage of subjects having CR or PR will be determined by the investigator assessment of radiographic disease assessments per RECIST v1.1.
  - AML/MDS: ORR, defined as the proportion of subjects who achieve CR or CRi per the International Working Group Response Criteria for Acute Myeloid Leukemia or the International Working Group Response Criteria for MDS, as applicable.
- PK parameters of INCB059872 in plasma: C_{max}, T_{max}, C_{min}, $AUC_{0\text{-}t}$, $t_{½}$, and Cl/F.

[redacted]

[redacted]

3. SUBJECT ELIGIBILITY

Potential subjects include those with advanced or metastatic malignancies who are ineligible for all therapeutic options that are standard of care or known to confer clinical benefit, or who refuse these treatments.

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

3.1. Subject Inclusion Criteria

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

1. Male or female subjects, age 18 years or older.
2. Presence of measurable disease that has been confirmed by histology or cytology. Myelofibrosis subjects must have palpable spleen of ≥ 5 cm below the left subcostal margin on physical examination at the screening visit.
3. The following malignancy types will be included in each of the treatment groups:

	Treatment Group	Malignancy Histology
Part 1 (Dose Escalation)	A	AML or MDS
	B	SCLC (other solid tumors, eg, endocrine tumors, are allowed with medical monitor approval)
Part 2 (Dose Expansion)	A1	Relapsed/refractory AML or MDS
	A2	MF (PMF, PPV-MF, and PET-MF)
	B1	SCLC
	B2	Ewing's sarcoma and poorly differentiated neuroendocrine tumors
Parts 3 and 4 (Combination Dose Escalation/Expansion)	C/C1	Relapsed/refractory AML
	D/D1	Newly diagnosed, treatment-naive AML, or MDS who are unfit to tolerate standard intensive chemotherapy at study entry and who are eligible to receive azacitidine as first-line therapy for the disease under study.
	E/E1	SCLC previously progressed on platinum-based treatment

4. Subjects must meet specific disease and treatment criteria as follows:
   - TG A/A1/A2, TG B/B1/B2, TG C/C1, and TG E/E1: The subject must not be a candidate for potentially curative therapy or standard-of-care approved therapy.
   - TG A2: The subjects must have confirmed diagnosis of primary MF (PMF), post–polycythemia vera MF (PPV-MF), or post–essential thrombocythemia MF (PET-MF) according to revised WHO 2016 criteria.

- TG D/D1:
  Subjects with newly diagnosed, treatment-naive AML who are unfit to tolerate standard intensive chemotherapy at study entry based on at least 1 of the following criteria (Ferrara et al 2013):
  - Age ≥ 75 years old.
  - History of congestive heart failure or documented ejection fraction ≤ 50%.
  - Pulmonary disease with diffusing capacity of the lungs for carbon monoxide ≤ 65% or FEVI ≤ 65%, or dyspnea at rest or requiring oxygen.
  - Any other comorbidity that the physician judges to be incompatible with intensive chemotherapy.

  OR

  Subjects with newly diagnosed, treatment-naïve, IPSS-R intermediate or higher risk disease MDS who have at least 5% bone marrow blasts, who are unfit to tolerate standard intensive chemotherapy at study entry, and who are eligible to receive azacitidine as first-line therapy for the disease under study.
  - The following treatments for prior lower risk MDS are acceptable: Revlimid®, low-dose cytarabine, and growth factors.
- TG E/E1: The subjects in TG E must have previously received platinum-based therapy, but additional lines of therapies are allowed. The subjects in TG E1 must not have received more than 1 previous line of therapy for locally advanced or metastatic SCLC. The previous line of therapy must be a platinum-based therapy, and the subjects must have progressed on or after this treatment.

5. Willingness to undergo a pretreatment bone marrow biopsy or aspirate (AML/MDS/MF) during screening (may be waived with medical monitor approval). Subjects with solid malignancies must have baseline archival tumor specimen available: a tumor block or approximately 15 slides from biopsy or resection of primary tumor or metastasis that are < 2 years old (specimens > 2 years old may be accepted with medical monitor approval).
6. ECOG performance status 0 to 2 (see Appendix E).
7. Willingness to avoid pregnancy or fathering children based on the following criteria:
   a. Woman of non-childbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy, ≥ 12 months of amenorrhea.)
   b. Woman of childbearing potential who has a negative serum pregnancy test at screening and before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subjects and their understanding confirmed.
   c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subjects and their understanding confirmed.

3.2. Subject Exclusion Criteria

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

1. Receipt of anticancer medications, anticancer therapies, or investigational drugs within the following interval before the first administration of study drug (requirement may be waived with medical monitor approval):
   a. < 5 half-lives or 14 days, whichever is longer, for any investigational agent
   b. < 5 half-lives for all other anticancer medications
   c. < 6 weeks for mitomycin-C or nitrosoureas
2. Any unresolved toxicity ≥ Grade 2 from previous anticancer therapy except for stable chronic toxicities (≤ Grade 2) not expected to resolve.
3. All treatment groups: prior receipt of an LSD1 inhibitor therapy. Parts 3 and 4 TG E/E1: prior receipt of anti–PD-1, anti–PD-L1, or anti–PD-L2 antibody.
4. Any of the following laboratory results at screening without transfusions and hematopoietic growth factor support in solid tumors (no lower limits in AML and MDS, or in MF with medical monitor approval):

Laboratory Parameter	Value
Absolute neutrophil count ($\times 10^9$/L)	< 1.5
Hemoglobin (g/dL)	< 9.0
Platelet count ($\times 10^9$/L)	< 100

5. Laboratory and medical history parameters outside Protocol-defined range unless associated with primary malignancy or metastatic disease and with medical monitor approval:
   a. Total bilirubin > 1.5 × institutional upper limit of normal (ULN) if no liver metastases or > 3 × ULN in the presence of liver metastases or presence of documented Gilbert syndrome (unconjugated hyperbilirubinemia).
   b. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.0 × institutional ULN.
   c. Creatinine clearance < 60 mL/min based on the institutional formula.
6. History or evidence of bleeding disorder requiring treatment.
7. History or presence of an abnormal ECG that in the investigator's opinion is clinically meaningful. A screening QTc interval > 470 milliseconds, as corrected by Fridericia, is excluded. For subjects with an intraventricular conduction delay (QRS interval 120 milliseconds), the JTc interval may be used in place of the QTc with sponsor approval. Subjects with left bundle branch block are excluded.
8. Prior radiotherapy within 2 weeks of study treatment. Subjects must have recovered from all radiation-related toxicities, including radiation pneumonitis, and not require corticosteroids. Evidence of fibrosis within a radiation field from prior radiotherapy is permitted with medical monitor approval. A 1-week washout period is permitted for palliative radiation to non–central nervous system (CNS) disease with medical monitor approval.

9. Unless approved by the medical monitor, allogeneic hematopoietic stem cell transplant within 6 months before treatment, or active graft-versus-host-disease after allogeneic transplant, or receipt of immunosuppressive therapy following allogeneic transplant within 2 weeks of Cycle 1 Day 1 (prednisone ≤ 10 mg/day is allowed).
10. Unless approved by the medical monitor, autologous hematopoietic stem cell transplant within 3 months before treatment.
11. History of human immunodeficiency virus infection.
12. Untreated brain or CNS metastases or brain/CNS metastases that have progressed (eg, evidence of new or enlarging brain metastasis or new neurological symptoms attributable to brain/CNS metastases). Subjects with previously treated and clinically stable brain/CNS metastases and who are off all corticosteroids for ≥ 4 weeks are eligible.
13. History of clinically significant or uncontrolled cardiac disease, including recent history (within 6 months) of unstable angina, acute myocardial infarction, New York Heart Association Class III or IV congestive heart failure, or arrhythmia requiring therapy.
14. Pregnant or nursing women or subjects expecting to conceive or father children within the projected duration of the study, starting with the screening visit through completion of safety follow-up visit.
15. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
16. Chronic or current active infectious disease requiring systemic antibiotics or antifungal or antiviral treatment, unless approved by sponsor medical monitor.
17. Current use of prohibited medication as described in Section 5.6.2.
18. Inability or unlikeliness to comply with the dose schedule and study evaluations, in the opinion of the investigator.
19. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
20. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
21. Inability to comprehend or unwilling to sign the informed consent form (ICF).
22. Inability to swallow and retain oral medication.
23. Evidence of active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
24. TG E/E1: Active, known, or suspected autoimmune disease. Subjects are permitted to enroll with vitiligo, diabetes mellitus, resolved childhood asthma/atopy, residual hypothyroidism due to an autoimmune immune condition only requiring thyroid hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.
25. TG C/C1: known allergy or reaction to any component of ATRA.
26. TG D/D1: known allergy or reaction to any component of azacitidine.
27. TG E/E1: known allergy or reaction to any component of nivolumab.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label, dose-escalation/dose-expansion study of the LSD1 inhibitor INCB059872 as a monotherapy and combination therapy in subjects with advanced malignancies. Subjects will receive INCB059872 doses QOD on a 28-day continuous therapy schedule; if QOD is well-tolerated, the next dose may be administered at a different dosing regimen (ie, QD) but will not exceed the 100% dose escalation for a total daily dose. As illustrated in Figure 1, the study will be conducted in 4 parts: Parts 1 and 2 will evaluate INCB059872 as monotherapy, with Part 1 for dose escalation and Part 2 for dose expansion, and Parts 3 and 4 will evaluate INCB059872 in combination with select therapies, with Part 3 for combination dose escalation and Part 4 for combination dose expansion. Part 1 (monotherapy dose escalation) will determine the starting dose(s) of INCB059872 for dose expansion, based on MTD. The recommended dose(s) will be taken forward into Part 2 (monotherapy dose expansion). The initiation of Part 2 will be based on further review of the ongoing clinical study and preclinical data of INCB059872 and information from literature. Part 3 (dose escalation of INCB059872 in combination therapy) will be initiated after the MTD in Part 1 is determined. Part 4 (dose expansion of INCB059872 in combination therapy) will explore the dose(s) confirmed in Part 3 and may be different based on combination therapy and/or tumor type.

4.1.1. Monotherapy Dose Escalation (Part 1)

Approximately 24 subjects will be enrolled into each dose-escalation treatment group.

Treatment Group A will enroll subjects with AML or MDS. The enrollment in TG B is prioritized for SCLC. Enrollment of subjects with other solid malignancies (eg, endocrine tumors) is allowed with the sponsor medical monitor approval.

Dose escalation for TG A and TG B in Part 1 will proceed independently, with each treatment group following a 3 + 3 design. The starting dose of INCB059872 for TG A and TG B will be 2 mg QOD. A minimum of 3 subjects will initially be enrolled in each treatment group in Part 1, and each subject will be observed for a DLT observation period of 1 cycle (28 days) before the next dose cohort begins enrollment. Subjects must have taken at least 75% of the cohort-specific dose (at least 11 doses for QOD schedule or at least 21 doses for QD schedule) in the first 28 days of study treatment or have had a DLT to be considered evaluable. Subjects who are not evaluable will be replaced. The dose will be escalated by up to 100% if none (0) of the first 3 evaluable subjects enrolled has a DLT. Dose escalation should proceed in smaller increments (ie, by no more than 50%) if a DLT is observed, or if 2 or more subjects at a given dose level experience Grade 2 or higher AEs (unless they are clearly and incontrovertibly due to an alternative cause).

If 1 of the first 3 evaluable subjects enrolled has a DLT, the cohort will be expanded to include 3 additional evaluable subjects, and if no DLT occurs in the additional 3 subjects, then the dose will be escalated by up to 100%. Otherwise, if 2 subjects in a cohort of 3 or 6 subjects experience DLTs, the MTD will be deemed to be exceeded. An interim lower dose level may be explored if the dose increment has been 100%. The MTD will be defined as 1 dose level below

the dose level at which one-third or more subjects experience DLTs. Upon the aggregate review of overall safety, PK, [redacted] and efficacy, a recommended dose (per tumor type) will be determined to maximize the clinical benefit/risk margin.

4.1.2. Monotherapy Dose Expansion (Part 2)

Upon identification of the recommended dose(s), up to 4 expansion cohorts per tumor type of approximately 15 subjects each may begin enrollment to further determine safety, tolerability, efficacy, PK, [redacted] of the selected dose(s). Treatment Group A1 will enroll subjects with AML or MDS (based on emerging data, the sponsor may decide to enroll specific subtypes of AML). Subjects in this A1 will have an opportunity to switch their treatment to a combination dose that is tested and found safe. Only subjects who have stable disease or better response for ≥ 3 months on monotherapy will be allowed to do so. Treatment Group A2 will enroll subjects with MF (PMF, PPV-MF, and PET-MF). Treatment Group B1 will enroll subjects with SCLC. Treatment Group B2 will enroll subjects with Ewing's sarcoma and poorly differentiated neuroendocrine tumors.

The selected doses for each treatment group are as follows:

- TG A1 dose will be 4 mg QD based on the safety and tolerability assessment in TG A (Part 1).
- TG A2, TG B1, and TG B2 doses will be 3 mg QOD based on the safety and tolerability assessment in TG B (Part 1).

A study of the effect of food on the PK of INCB059872 will be conducted in Part 2, TG B1 only.

If ≥ 5 subjects in the first 15 subjects of any cohort cumulatively (or more than 33% of subjects in cohorts larger than 15 subjects) experience DLTs during Cycle 1, then further enrollment to the cohort will be stopped, and a lower dose level may be explored.

Individual dose titration will be permitted according to Protocol-defined safety parameters. Subjects will continue to receive INCB059872 in 28-day cycles until a withdrawal criterion is met.

4.1.3. Combination Dose-Finding (Part 3)

Part 3 enrollment will be initiated after the MTD has been determined in Part 1 and will include dose-finding to evaluate safety and tolerability of the combinations. Enrollment of Part 3 will occur in parallel with Part 2. Dose-finding will use a 3 + 3 design to evaluate different doses of INCB059872 in combination with other therapies in the following treatment groups:

- Combination TG C: INCB059872 in combination with ATRA in subjects with relapsed/refractory AML. The starting dose for INCB059872 in this cohort will be 2 mg QD (2 dose levels below the recommended dose for monotherapy expansion in TG A1).
- Combination TG D: INCB059872 in combination with azacitidine in subjects with newly diagnosed, treatment-naive AML or MDS with at least 5% bone marrow blasts and IPSS-R intermediate or higher risk disease who are unfit to tolerate standard intensive chemotherapy at study entry and who are eligible to receive azacitidine as first-line therapy for the disease under study. The starting dose for INCB059872 in

this cohort will be 2 mg QD (2 dose levels below the recommended dose for monotherapy expansion in TG A1).

- Combination TG E: INCB059872 in combination with nivolumab in subjects with advanced SCLC who previously progressed on platinum-based treatment. The starting dose for INCB059872 in this cohort will be 3 mg QOD (the recommended dose for monotherapy expansion in TG B1).

The starting dose of INCB059872 in the combination treatment groups was based upon the tolerability of INCB059872 monotherapy identified in Part 1 of this study. Doses of the combination agents will be selected from conventional dose regimens and will remain the same for all dose-finding and dose-expansion cohorts. INCB059872 doses will not exceed the monotherapy MTD identified in Part 1. A minimum of 3 subjects will initially be enrolled in each treatment group in Part 3, and each subject will be observed for a DLT observation period of 1 cycle (28 days) before the next dose cohort or expansion to Part 4 begins enrollment. Subjects must have taken at least 75% of the cohort-specific dose (at least 11 doses for QOD schedule or at least 21 doses for QD schedule) in the first 28 days of study treatment or have had a DLT to be considered evaluable. Subjects who are not evaluable will be replaced.

If tolerated, the combination treatment groups will escalate independently and in parallel until the MTD or optimal doses of the combinations are identified and will be followed by independent expansion cohorts at the selected dose(s). If the starting dose is not tolerated in any of the combination treatment groups, a lower dose of INCB059872 may be explored; otherwise, higher doses found to be safe and tolerable in Part 1 may be explored. The sponsor, in consultation with participating investigators, may elect to expand a dose cohort(s) deemed tolerable, to up to 12 subjects, in order to obtain supplemental PK, [redacted], and safety data.

4.1.4. Combination Dose Expansion (Part 4)

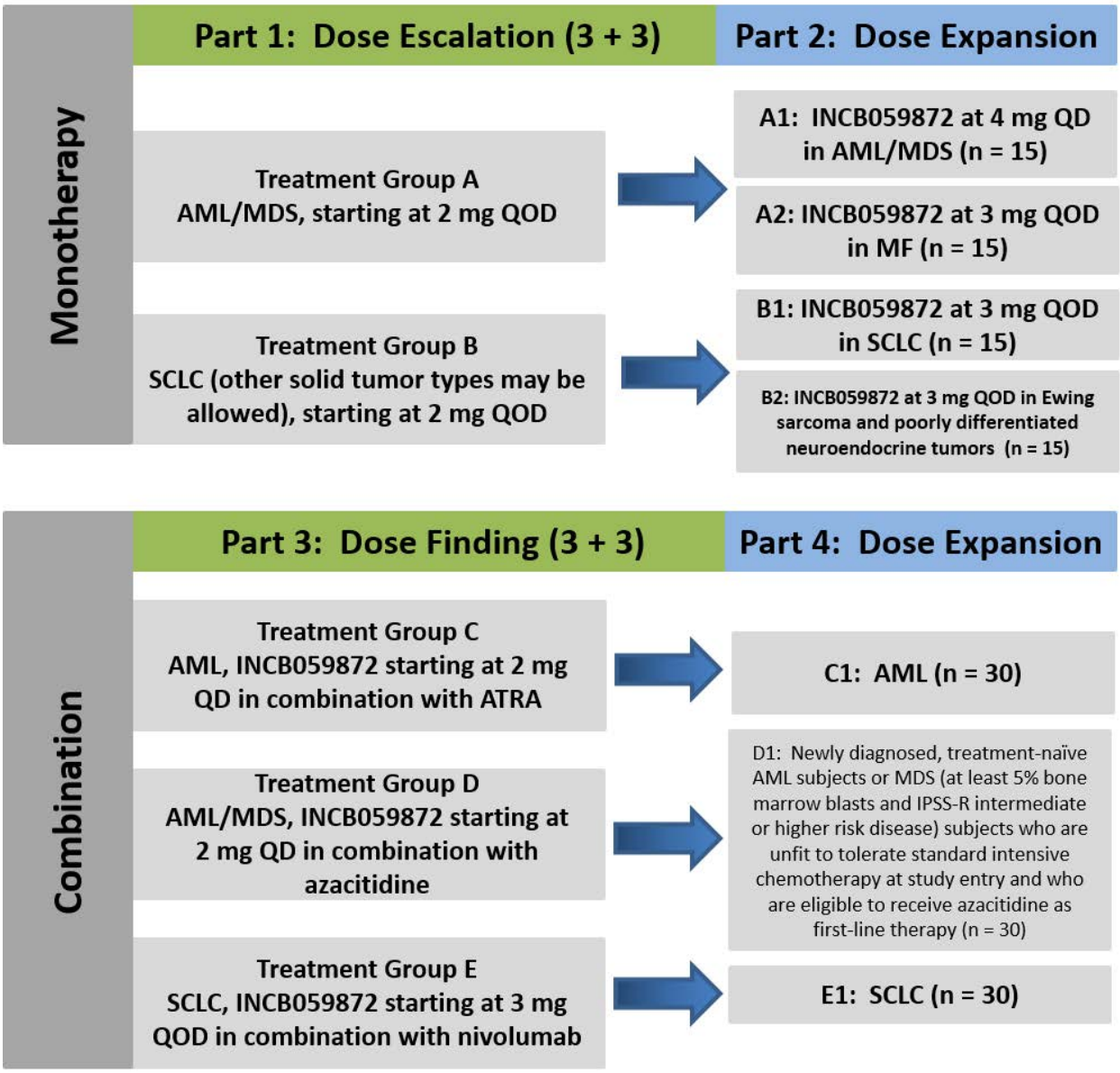
Upon identification of the recommended dose(s) for each treatment combination in Part 3, expansion cohorts of approximately 30 subjects in each treatment group may begin enrollment to further determine safety, tolerability, efficacy, PK, [redacted] of the selected dose(s).

- Combination TG C1: INCB059872 in combination with ATRA using the regimen identified in Part 3 in subjects with relapsed/refractory AML.
- Combination TG D1: INCB059872 in combination with azacitidine using the regimen identified in Part 3 in subjects with newly diagnosed, treatment-naive AML or MDS with at least 5% bone marrow blasts and IPSS-R intermediate or higher risk disease who are unfit to tolerate standard intensive chemotherapy at study entry and who are eligible to receive azacitidine as first-line therapy for the disease under study.
- Combination TG E1: INCB059872 in combination with nivolumab using the regimen identified in Part 3 in subjects with advanced SCLC who previously progressed on platinum based treatment.

In Part 4, a stopping rule for futility is planned for each combination dose expansion treatment group. The futility analyses for combination TGs will be conducted when 15 subjects for each disease type have been treated and evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. The futility

analyses for TG D1 will be conducted when the first 15 subjects with AML or when the first 15 subjects with MDS have been treated.

Figure 1: Study Design



4.2. Measures Taken to Avoid Bias

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

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Approximately 215 subjects will be enrolled in this study as follows:

- Part 1 will enroll approximately 24 subjects into each dose-escalation treatment group. This may vary due to the number of cohorts required to determine the target dose(s).
- Part 2, approximately 15 subjects will be enrolled in each of the 4 treatment groups.
- Part 3 will enroll approximately 15 subjects total for all three treatment groups. This number may vary due to the number of cohorts required to determine the optimal combination dose. The sponsor, in consultation with participating investigators, may elect to expand a dose cohort(s) deemed tolerable, to up to 12 subjects, in order to obtain supplemental PK, [redacted], and safety data.
- Part 4 will enroll approximately 30 subjects in TG C1, TG D1, and TG E1.

4.3.2. Replacement of Subjects

In Parts 1 and 3, if a subject is not evaluable (ie, did not receive at least 75% of cohort-specific dose within the first 28 days of study treatment), another subject will be enrolled at this dose level. Subjects who report DLTs will be considered evaluable for the purpose of determining the safety and tolerability of the dose.

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Each subject enrolled in the study may continue to receive study treatment in continuous 28-day cycles. If the subject discontinues INCB059872, the treatment period will end and the subject will enter the follow-up period (see Section 6.4). Study participation is expected to average approximately 6 months per individual subject.

4.5. Overall Study Duration

The study begins when the first subject signs the informed consent form. The end of the study will occur when all subjects have discontinued study drug and have completed applicable follow-up assessments.

If there have been ≤ 2 subjects on study for more than 6 months, a database lock of the study may occur to allow the analysis of the study data. Any remaining subjects may continue to receive study treatment and be seen by the investigator per usual standard of care for this population. The investigator will be expected to monitor for and report any SAEs, AEs of special interest, and pregnancies, as detailed 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.

5. TREATMENT

INCB059872 will be self-administered orally QOD or QD on a 28-day cycle. In each cycle of the QOD dosing schedule, subjects should receive 14 doses of INCB059872. In each cycle of the QD dosing schedule, subjects should receive 28 doses of INCB059872. Tablets will be available in 1 mg strength. The initial starting dose for Part 1 will be 2 mg QOD. The initial starting dose for other parts of the study will be based on the aggregate data review of Part 1.

For QOD administration, if a dose is missed by more than 24 hours, the subject should skip the dose and take the next scheduled dose at the usual time. For QD administration, if a dose is missed by more than 4 hours, the subject should skip the dose and take the next scheduled dose at the usual time. INCB059872 tablets should be taken on an empty stomach if possible (refrain from food consumption during the period 2 hours before and 1 hour after taking INCB059872). For subjects participating in the food-effect portion of the study in Part 2, TG B1, a high-fat, high-calorie meal will be consumed within 30 minutes before taking INCB059872 on Cycle 2 Day 1.

Alternative dosing regimens (ie, QD) may be explored based on emerging PK/[redacted] and safety data.

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Study sites will enter subject demographic and baseline data into the Interactive Response Technology (IRT) in order to receive a subject number at the time of the subject enrollment. Sites will have to update the IRT system at each visit in order to receive the treatment allocation.

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

This is a nonrandomized study; subjects will be assigned the same dose and treatment regimen in a particular treatment group. The investigator or designee will pull the correct number of bottles of study drug from their stock and dispense the study drug to the subject. All subsequent dispensing of study drug should follow this process. Refer to the IRT manual for detailed information.

For subjects who signed an ICF but are not allocated and for subjects who are allocated but were not treated, refer to the eCRF Completion Guidelines for instruction on which eCRFs to complete.

5.1.2. Randomization and Blinding

Not applicable.

5.2. Study Drug Materials and Management

5.2.1. INCB059872

5.2.1.1. Supply, Packaging, and Labeling

Study drug will be supplied as 1 mg tablets of INCB059872. All tablet excipients comply with the requirements of the applicable compendial monographs (Ph Eur, USP/NF; refer to the IB).

INCB059872 will be provided as 1 mg tablets packaged in high-density polyethylene bottles. No preparation is required.

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country and will state "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

5.2.1.2. Storage

Bottles of tablets should be stored in a refrigerator and maintained at a temperature between 2°C and 8°C (36°F to 46°F).

5.2.1.3. Instruction to Subjects for Handling Study Drug (INCB059872)

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

- To store the study drug in the refrigerator.
- To only remove from the study drug bottle/kit the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To report any missed doses.
- To take study drug immediately upon awakening or 2 hours after completing a meal with a glass of water.
- If the subject vomits after taking study drug, the subject should not take another dose.
- To keep study drug in a safe place and out of reach of children.
- To bring all used and unused study drug kits to the site at each visit.
- Subjects who do not take their dose in the morning as instructed should plan to take the dose in the evening, with the same fasting parameters applied.

- If a dose is missed by more than 24 hours on a QOD schedule, that dose should be skipped, and the next scheduled dose should be administered at the usual time.
- If a dose is missed by more than 4 hours on a QD schedule, that dose should be skipped, and the next scheduled dose should be administered at the usual time.

5.2.2. Conventional Care Drugs

Every effort should be made by the sites to procure the commercially available and packaged product. However, Incyte will provide certain reference therapy or therapies, such as tretinoin capsules or azacitidine or nivolumab where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to the therapy or therapies.

5.2.2.1. Tretinoin Capsules

In Parts 3 and 4 TG C and TG C1, Tretinoin (ATRA) capsules will be administered as an open-label commercial product in accordance with local prescribing information at a dose of 45 mg/m^2 per day. The daily dose should be administered as 2 evenly divided doses. Drug is available in 10 mg capsules and should be stored in accordance with the package insert. Toxicity associated with tretinoin capsules will be managed per instruction in the package insert.

5.2.2.2. Azacitidine

In the Parts 3 and 4 TG D and TG D1, azacitidine will be administered in accordance with local prescribing information as an open-label commercial product at a starting dose of 75 mg/m^2 SC or IV for 7 days during the first 9-day or less period (ie a 2-day break allowed on weekend, if needed) of each 28-day treatment cycle. Toxicity associated with azacitidine dosing will be managed per instructions in the package insert (Vidaza PI 2014).

Investigative sites must provide subjects with administration and storage instructions, as per package insert or institution standard, for azacitidine SC syringes dispensed to subjects for administration away from investigative site.

5.2.2.3. Nivolumab

Nivolumab will be administered at a dose of 3 mg/kg as an IV infusion over 60 minutes every 2 weeks (Q2W). Toxicity associated with immune reactions or infusion reactions will be managed following guidance in Sections 5.4.8 and 5.4.9.

Nivolumab must be used in accordance with the storage conditions and shelf life in the manufacturer's approved label.

5.3. Treatment Compliance

5.3.1. Treatment Compliance With INCB059872

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 INCB059872 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 all study drugs 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.

5.3.2. Treatment Compliance With ATRA, Azacitidine, and Nivolumab

Compliance with ATRA 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 all study drugs 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.

Azacitidine and nivolumab may be administered as an IV infusion by site personnel. Receipt of infusions will be documented by the site staff and monitored by the sponsor/designee. Azacitidine may also be administered SC away from the investigative site and should be documented to ensure drug accountability.

5.4. Treatment Interruptions and Adjustments

5.4.1. Dose Modifications of INCB059872

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

Subjects enrolled in the dose-escalation portion of the study will have the option of escalating to a dose found to be tolerated in a subsequent cohort either within the same or alternative regimen.

Subjects enrolled in TG C and TG D who have a bone marrow blast response (at least MFLS for AML, and CR or Marrow CR for MDS) may be able to explore different and less intensive dosing regimens to allow for hematologic recovery, especially platelet recovery, as approved by the medical monitor, such as switching from QD dosing to QOD dosing. If the subject shows signs of losing the response and if deemed safe by the investigator, then the subject is allowed to revert to the prior dose and dosing schedule, but a more intensive dosing regimen than the starting dose is not allowed.

Dosing modifications due to response only is not allowed during the DLT evaluation period. In addition to dose interruption and reduction, dosing schedule modification (eg, switching from QD to QOD dosing) is also allowed for toxicity management per medical monitor approval.

5.4.2. Dose Modifications of Conventional Care Agents

Decisions regarding dose reduction of conventional care agents (ATRA, azacitidine, nivolumab) should be made following the guidelines in Table 5 and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study drug and the subject's underlying condition as well as in accordance with local prescribing information.

5.4.3. Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose of INCB059872

Dose-limiting toxicity will be defined as the occurrence of any of the toxicities in Table 4 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 (NCI 2010). Subjects who receive at least 75% of the planned doses (eg, 11 of 14 doses for QOD schedule) of study drug at the level assigned or have a DLT will be considered evaluable for determining tolerability of the dose. Subjects who cannot complete 75% of the planned doses of study drug for reasons not due to toxicities related to study drug will not be considered evaluable for the purposes of determining the MTD and will be replaced.

Individual subject dose reductions may be made based on events observed at any time during treatment with study drug; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD of INCB059872, decisions will be made based on events that are observed from the first day of study drug administration through and including the final day of Cycle 1 (Day 28). A lower MTD may subsequently be determined based on relevant toxicities that become evident after Day 28.

Table 4: Definition of Dose-Limiting Toxicity

Nonhematologic toxicity
• Any ≥ Grade 3 nonhematologic toxicity EXCEPT: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. – Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions).
Hematologic toxicity
• Anemia : Grade 4, unexplained by underlying disease • Neutropenia: – For solid tumors: Grade 4 that does not recover to ≤ Grade 3 in ≤ 7 days after dose interruption. – For AML/MDS/MF: Grade 4 with a hypocellular bone marrow lasting ≥ 6 weeks after the start of a course in the absence of residual disease. • Febrile neutropenia (for solid tumors only): absolute neutrophil count < 1.0×10^9/L with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour. • Thrombocytopenia: – For solid tumors: Any Grade 4 or Grade 3 with bleeding or any requirement of platelet transfusion. – For AML/MDS/MF: Grade 3 or higher with clinically significant bleeding or any requirement of platelet transfusion outside of institutional practice.
Other toxicities not meeting criteria above
• While the rules for adjudicating DLTs in the context of dose escalation are specified above, an AE not listed above may be defined as a DLT after a consultation with the sponsor and investigators, based on the emerging safety profile.

5.4.4. 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.

5.4.5. 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 2 weeks. During follow-up, subjects should be seen as often as medically indicated to assure safety.

5.4.6. Procedures for Cohort Review and Dose Escalation

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

5.4.7. Criteria and Procedures for Dose Interruptions and Adjustments of INCB059872

Study treatment may be delayed up to 2 weeks (14 days) to allow for resolution of toxicity with the exception of irAEs in subjects enrolled in TG E/E1 (see Table 6 for the management of irAEs). Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any subject whose treatment has been delayed for more than 14 days before restarting study treatment.

Because subjects may enter the study with extensive pretreatment and/or severe bone marrow infiltration by the primary disease, these dose reduction rules are provided as guidelines (see Table 5). Individual decisions regarding dose reduction should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study drug and the subject's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules.

Table 5: Guidelines for Interruption and Restarting of Study Drug

Chemistry			
Adverse Event			**Action Taken**
• AST and/or ALT is > 3.0 × ULN and < 5.0 × ULN; repeat in 1 week and if persistent or increasing or • AST and/or ALT is > 5.0 AND < 20 × ULN Note: In subjects with liver metastasis-related elevations as baseline, contact sponsor to discuss clinical management and possible dose reductions.			1. Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except by approval of the medical monitor. 2. Restart study drug at same dose and monitor as clinically indicated. If rechallenge is positive with AST and/or ALT elevation > 3.0 × ULN, restart study drug at next lower dose (or at 25% reduction, rounded down to the nearest pill strength); monitor as clinically indicated.
• AST and/or ALT is > 20 × ULN			Discontinue treatment.
• ALT > 3.0 × ULN, alkaline phosphatase < 2 × ULN, and bilirubin ≥ 2.0 × ULN (Hy's Law) and no other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) know to be hepatotoxic.			Discontinue treatment.
Hematology			
Parameter	**Tumor Types**	**Adverse Event**	**Action Taken**
Platelets ($\times 10^9$/L)	Solid tumors	≥ 25 to < 50	1. If symptomatic (eg, clinically significant bleeding), discontinue. 2. If asymptomatic, hold until resolved to ≥ 75 and restart study drug at next lower dose and monitor.
		< 25	1. If symptomatic (eg, clinically significant bleeding), discontinue. 2. If asymptomatic, hold until resolved to ≥ 75, then restart study drug at next lower dose and monitor.
	AML/MDS/MF	N/A	1. Thrombocytopenia should be managed per institutional standard, relevant to the underlying disease, including initiating or increasing the frequency of platelet transfusion. If there is a suspected causal relationship to INCB059872 in the setting of a decreasing platelet count, hold INCB059872 and/or reduce INCB059872 dose for any of the following: a. Platelet decreased > 50% compared with baseline and below 25 × 10^9/L. b. Accompanied by any sign of bleeding. c. Platelet transfusion refractory. 2. Discontinue if clinically significant bleeding suspected to be related to study treatment. 3. Discuss with medical monitor for dose modifications under any other situations not discussed above, if needed.

Table 5: Guidelines for Interruption and Restarting of Study Drug (Continued)

Hematology (Continued)			
Parameter	**Tumor Types**	**Adverse Event**	**Action Taken**
Absolute neutrophil count ($\times 10^9$/L)	Solid tumors	≥ 0.5 to < 1.0	1. Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≥ 1.0 except by approval of the medical monitor. Granulocyte colony-stimulating factor is allowed in the management of neutropenia 2. Restart study drug at next lower dose and monitor.
		< 0.5	1. If symptomatic (eg, infection), discontinue 2. If asymptomatic, interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≥ 1.0 except by approval of the medical monitor. Granulocyte colony-stimulating factor is allowed in the management of neutropenia. Restart study drug at the next lower dose and monitor.
	AML/MDS/MF	N/A	Neutropenia should be managed per institutional standard, relevant to the underlying disease. If there is a suspected causal relationship to INCB059872 in the setting of a decreasing neutrophil count, hold INCB059872 and discuss with the medical monitor.
Hemoglobin (g/dL)	All tumors	< 6.5	1. Hold until resolved to ≥ 8.0, restart at next lower dose, and monitor. 2. If recovery to ≥ 8.0 does not occur within 14 days of dose interruption or is refractory to transfusion support, discontinue study drug treatment(s) and follow-up per Protocol.
Leukocytosis	AML/MDS	N/A	Leukocytosis due to progression of underlying disease should be managed per institutional standard.
Other toxicities			
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care.			1. Interrupt study drug up to 2 weeks (14 days), until toxicity resolves to $\leq$ Grade 1. 2. Restart study drug at the next lower dose and monitor as clinically indicated.
• Any recurrent toxicity after 2 dose reductions.			Discontinue study drug administration and follow-up per Protocol. (Exceptions require approval of sponsor.)
• Any Grade 4 toxicity.			Discontinue study drug administration and follow-up per Protocol.

5.4.8. Management of Immune-Related Adverse Events

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

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of drug-related AEs with potential immunologic etiology are outlined in Table 6. Detailed supportive care guidelines for specific irAEs can be in found in Appendix H. Nivolumab may have specific irAE management guidelines within the package insert; the treating investigator may use labeled guidance or institutional guidelines for the management of irAEs if preferred. For each AE, attempts should be made to rule out other causes, including but not limited to metastatic disease or bacterial or viral infection, which might require specific supportive care.

Table 6: General Approach to Handling Immune-Related Adverse Events

irAE	Withhold/Discontinue Nivolumab and INCB059872	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	Withhold nivolumab. May withhold INCB059872 per investigator's discretion. Discontinue if unable to reduce corticosteroid dose to < 10 mg/day of prednisone or equivalent within 6 weeks of toxicity.	May return to treatment if improves to Grade 1 or resolves within 6 weeks. If AE resolves within 4 weeks, subject may restart at the same dose and schedule for both nivolumab and INCB059872. For an AE that does not resolve within 4 weeks, nivolumab should be reduced 1 dose level but INCB059872 may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grades 3	Withhold or discontinue nivolumab and INCB059872. Discontinue if unable to reduce corticosteroid dose to < 10 mg/day of prednisone or equivalent within 6 weeks of toxicity.	Any restart of study treatment must be discussed with medical monitor before restarting treatment.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1 to 2 mg/kg of prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to ≤ Grade 1 and tapered over at least 4 weeks in most cases.
Grade 4	Discontinue nivolumab and INCB059872.	Not applicable. Any exceptions require medical monitor approval.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to ≤ Grade 1 and tapered over at least 4 weeks in most cases.

5.4.9. Management of Infusion Reactions

Subjects in TG E/E1 may experience an infusion reaction associated with administration of study treatment. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Nivolumab infusion reactions should be managed according to guidance within the package insert; the treating investigator may use labeled guidance or institutional guidelines for the management of infusion reactions if preferred.

5.4.10. Criteria for Permanent Discontinuation of INCB059872

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

- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- An AE requiring more than 2 dose reductions.
- Persistent AE requiring a delay of therapy for more than 2 weeks (14 days) unless a greater delay has been approved by the sponsor.

5.4.11. Criteria and Procedures for Dose Increases of INCB059872

Intrasubject dose escalation will be permitted with sponsor preapproval in the following circumstances:

- The Protocol eligibility criteria are met at the time of escalation.
- The subject has received ≥ 4 cycles of study drug without drug-related toxicity ≥ Grade 2.
- The next higher dose level has been determined to be safe based on the MTD criteria.
- The subject is willing to submit to the PK sampling and safety monitoring schedules as in Cycle 1 Day 15.
- In the opinion of the investigator, the subject does not have any concurrent condition or circumstance that would complicate the dose escalation or PK sampling, or pose increased risk to the subject.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

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

- The subject becomes pregnant.
- Consent is withdrawn. Note: Consent withdrawn means that the subject can no longer be followed. Subjects may choose to discontinue study treatment and remain in the study to be followed for disease progression.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- Unacceptable toxicity has occurred.
- Disease progression has occurred, except in the circumstance where, in the setting of otherwise stable disease, a medical procedure or radiation therapy is required to a single lesion, with medical monitor approval.

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

- If, during the course of the study, a subject is found not to have met eligibility criteria, 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, 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 last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the eCRF. In addition, the following steps should be followed (Note: These visits are described in Section 6):

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

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

5.6. Concomitant Medications

All concomitant medications and treatments must be recorded in the eCRF. Any prior medication received up to 28 days before the first dose of study treatment and 30 days after the last dose of study treatment, or until the subject begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF.

5.6.1. Restricted Medications

- If concomitant administration of an anticoagulant/antiplatelet medication is indicated, caution and enhanced monitoring are required.
  - History of thrombocytopenia and any concurrent INCB059872-related thrombocytopenia should be a factor in the choice of anticoagulant and dose.
- Hydroxyurea is restricted during the treatment periods of the study; however, it may be used to treat hyperleukocytosis per medical monitor approval.

5.6.2. Prohibited Medications

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

- Use of any anticancer drugs during study.
- Hydroxyurea is prohibited within 48 hours before initiation of study treatment during the screening period and within 24 hours before collection of [redacted].
- Aspirin in doses exceeding 81 mg/day.
- Use of potent inhibitors of CYP2D6 or potent inhibitors or inducers of CYP3A4 (Appendix B).

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (Table 7), and all laboratory assessments will be performed as indicated in Table 8. Table 9 presents a summary of clinical laboratory analytes to be assessed. The order of assessments is suggested by the order of mention within the schedule. See Section 7 for instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual.

Table 7: Schedule of Assessments

Procedure	Protocol Section	Screening	Treatment						EOT	Follow-Up		Notes
			Cycle 1				Cycles 2+			Safety	Disease Status	
		Days -28 to -1	Day 1	Day 8 (± 2 Days)	Day 15 (± 2 Days)	Day 22 (±2 Days)	Day 1 (± 2 Day)	Day 15 (± 2 Days)		30 Days (+5 Days)	Every 8-9 Wks	
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		
Physical examination/ body weight, height	7.5.2	X*	X	X	X	X	X	X	X	X		* Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only.
Vital signs	7.5.3	X	X	X	X	X	X	X	X	X		
12-lead ECG	7.5.4	X	X*	X**	X*				X	X		* Timed triplicate ECG (separated by 2-5 min); predose and 1, 2, and 6 hours postdose. ** Triplicate ECG (separated by 2-5 min) at 1 timepoint approximately 24 hours after last dose.
ECOG status	N/A	X	X	X	X	X	X	X	X	X		
[redacted]												
CT or MRI for solid tumors	7.6, 6.4.2	X					X*		X		X	* Every 8 weeks (± 7 days) from Cycle 1 Day 1.

Table 7: Schedule of Assessments (Continued)

Procedure	Protocol Section	Screening	Treatment						EOT	Follow-Up		Notes
			Cycle 1				Cycles 2+			Safety	Disease Status	
		Days -28 to -1	Day 1	Day 8 (± 2 Days)	Day 15 (± 2 Days)	Day 22 (±2 Days)	Day 1 (± 2 Day)	Day 15 (± 2 Days)		30 Days (+5 Days)	Every 8-9 Wks	
AML/MDS disease assessments	7.6, 6.4.2	X					X*		X		X	* Every 4 weeks from baseline; can be peripheral blood or bone marrow aspirate or biopsy.
MF disease assessments (spleen palpation)	7.6, 6.4.2	X	X				X*		X		X	* Every 4 weeks from Week 4 through Week 24 and every 12 weeks after Week 24.
MF disease assessments (bone marrow assessment)	7.6	X					X*					* Every 24 weeks.
MF subjects: MRI of the upper and lower abdomen and pelvis	7.6	X					X*					* Every 12 weeks from baseline; CT scan may be substituted if MRI is contraindicated.
[redacted]												
Review AEs	8.1	X	X	X	X	X	X	X	X	X		
Study drug dispensing	N/A		X				X*					* Drug dispensed on Day 1 of each cycle.

Table 7: Schedule of Assessments (Continued)

Procedure	Protocol Section	Screening	Treatment						EOT	Follow-Up		Notes
			Cycle 1				Cycles 2+			Safety	Disease Status	
		Days -28 to -1	Day 1	Day 8 (± 2 Days)	Day 15 (± 2 Days)	Day 22 (±2 Days)	Day 1 (± 2 Day)	Day 15 (± 2 Days)		30 Days (+5 Days)	Every 8-9 Wks	
Administer INCB059872 at site	N/A		X	X*	X*	X*	X**					* Subjects should not take drug at home but must bring medication; they will take their dose after initial PK blood draw. NOTE: Drug is not given on Day 8, but if on a dosing day, subject should follow rules above. ** TG B1 subjects for food-effect study.
Assess compliance	5.3			X	X	X	X	X	X			
Administer ATRA at site			X*	X*	X*	X*						* 45 mg/m^2 per day administered as 2 evenly divided doses; AM dose only in the clinic.
Administer azacitidine at site			X*	X*	X*	X*	X*					* 75 mg/m^2 SC or IV for7 days during the first 9-day or less period (ie, a 2-day break allowed on weekend, if needed) of each 28-day treatment cycle.
Administer nivolumab at site			X*		X*		X*	X*				* 3 mg/kg Q2W.
Distribute reminders	7.10.1	X	X	X	X	X	X	X				

CT = computed tomography; [redacted]; MRI = magnetic resonance imaging; [redacted]

Table 8: Schedule of Laboratory Assessments

Local Laboratory Tests	Protocol Section	Screening	Treatment						EOT	Safety Follow-Up	Notes
			Cycle 1				Cycles 2+				
			Day 1	Day 8 (± 2 Days)	Day 15 (± 2 Days)	Day 22 (±2 Days)	Day 1 (± 2 Day)	Day 15 (± 2 Days)		30 Days (+5 Days)	
Serum chemistries	Table 9	X	X*	X	X	X	X	X	X	X	* May be performed 3 days before the first dose.
Hematology*	Table 9	X	X**	X	X	X	X	X	X***	X	* Must be drawn twice a week for the first 2 weeks of study treatment. In addition to Cycle 1 Day 1 and Cycle 1 Day 8, hematology samples should be drawn at Cycle 1 Day 4 ± 1 day and Cycle 1 Day 11 ± 1 day. ** May be performed 3 days before the first dose. *** Must be drawn twice a week for 2 weeks after last dose.
Lipid panel	Table 9	X	X	X	X	X	X	X	X	X	
Coagulation panel	Table 9	X					X*		X		* Cycle 2 Day 1 and then every 3 cycles thereafter.
Hepatitis screening	Table 9	X									
Urinalysis	Table 9	X					X*				* Cycle 2 Day 1 and then every 3 cycles thereafter
Pregnancy test	Table 9	X*	X**						X**		All female subjects of childbearing potential. * Serum ** Urine
PK plasma (predose)	7.8.1		X	X	X	X	X*				Collect before morning dose of study drug. * Cycle 2 Day 1, only for food-effect testing in Part 2.
PK plasma TIMED (postdose)	7.8.1.1		X*		X*		X**				* Collect at 0.5, 1, 2, 4, and 6 hours after INCB059872 dose. Excess sample will be used for [redacted] analysis. ** Cycle 2 Day 1 only for food-effect study.

Table 8: Schedule of Laboratory Assessments (Continued)

Local Laboratory Tests	Protocol Section	Screening	Treatment						EOT	Safety Follow-Up	Notes
			Cycle 1				Cycles 2+				
			Day 1	Day 8 (± 2 Days)	Day 15 (± 2 Days)	Day 22 (±2 Days)	Day 1 (± 2 Day)	Day 15 (± 2 Days)		30 Days (+5 Days)	
Urine PK	7.8.2				X						Obtain a predose sample and store separately. Provide a complete urine output collection from Hour 0 (starting after morning dose) through 6 hours.
[redacted]											

Table 9: Local Laboratory Tests: Required Analytes

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

Differential count, including:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils

Absolute values must be provided for:
• WBC differential laboratory results
• Neutrophils</td><td>Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein</td><td>Hepatitis B surface antigen
Hepatitis B core antibody
HBV-DNA
HCV antibody
HCV-RNA</td><td>Prothrombin time/international normalized ratio
Partial thromboplastin time</td></tr>
<tr><td>Lipid Panel

Total cholesterol
Triglycerides
Low-density lipoprotein
High-density lipoprotein</td><td>Subjects With AML/MDS

Immunophenotyping
Cytogenetics

Subjects With MF

JAK-2 mutation status
Cytogenetics</td><td>Pregnancy Testing

Female subjects of childbearing potential require a serum test at screening and a urine pregnancy test before the first dose on Cycle 1 Day 1 and at EOT.
Pregnancy tests (serum or urine) should be repeated if required by local regulations.</td></tr>
</table>

Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.

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 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the subject's routine clinical management (eg, blood count, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 28 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. Treatment should start as soon as possible, but within 3 days after the date of enrollment. 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). (Note: For subjects who fail screening but are rescreened, a new subject number will be assigned.)

6.2. Treatment

The treatment period begins on the day the subject receives the first dose of study drug (Cycle 1 Day 1) through the point at which the investigator determines the subject will be permanently discontinued from study drug. Cycle 1 Day 1 must be no more than 28 days after the subject has signed the ICF and no more than 3 days after the date of registration. Dates for subsequent study visits will be determined based on this day and should occur within the specified visit windows noted in Table 7 and Table 8 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 Section 3.

Note: Day 15 visits beyond Cycle 4 may be optional (except for subjects in TG E/E1) per subject overall status and approval by the sponsor medical monitor.

6.3. End of Treatment

When the subject permanently discontinues study drug, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, 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 to 35 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Note that subjects will be required to submit to twice weekly blood draws in the 2 weeks after the last dose of study drug.

Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the follow-up visit, or until toxicities resolve, return to baseline, are deemed irreversible, or the subject initiates a new anticancer treatment, whichever occurs first. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this period.

If a subject is scheduled to begin a new anticancer therapy before the end of the 30-day safety follow-up period, the safety follow-up visit should be performed before new anticancer therapy is started.

6.4.2. Disease Status Follow-Up

Subjects who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should be assessed every 8 to 9 weeks by radiologic imaging (SCLC/solid tumors) or blood/bone marrow assessment (AML/MDS/MF) to monitor disease status. Every effort should be made to collect information regarding disease status until (whichever occurs first):

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

6.5. End of Study

The end of the study may be designated as the timepoint when all subjects have discontinued the study or the sponsor terminates the study.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

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

7.2. Interactive Response Technology Procedure

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

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening.

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication history will be collected at screening.

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 30 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.

7.5. Safety Assessments

7.5.1. 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.

7.5.2. Physical Examinations

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

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

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

7.5.2.1. Comprehensive Physical Examination

The comprehensive physical examination performed at screening 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.

7.5.2.2. Targeted Physical Examination

The targeted physical examination performed at all other visits 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.

7.5.3. Vital Signs

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

7.5.4. Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest. A single ECG is performed at the screening, EOT, and safety follow-up visits. Triplicate ECGs are performed on Cycle 1 Day 1 and Cycle 1 Day 15 at predose and 1, 2, and 6 hours postdose. A triplicate ECG is performed on Cycle 1 Day 8 approximately 24 hours after the last dose on Day 7; if a subject is being seen on Day 7 or Day 9 (study drug administration days), triplicate ECG should be performed before study drug administration. Note that triplicate ECGs should be performed with a 2- to 5-minute break between evaluations. Note that the timed schedule may change per emerging PK data.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate subject management; all ECGs will be collected and reviewed by a central ECG vendor. 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.

7.5.5. Laboratory Assessments

Sites will use their local laboratories for eligibility and ongoing safety assessments. Chemistry, hematology, coagulation panel, serology, lipid panel, and urinalysis will all be analyzed.

For MF subjects only: after 24 weeks, D15 visits of each cycle can be omitted, with medical monitor approval.

7.5.5.1. Pregnancy Testing

A pregnancy test will be required for all women of childbearing potential during screening, on Day 1 (before the first dose of study drug) and at the end of treatment visit. Serum or urine pregnancy tests will be conducted as outlined in Table 8, as medically indicated, or per country-specific requirement. Urine pregnancy tests will be done locally. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

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

7.6. Efficacy Assessments

Objective assessment of tumor status is required using appropriate disease-specific techniques, and the investigator's assessment will be used to determine responses and will be logged into the eCRF. For SCLC/solid tumors subjects, Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer et al 2009) will be used, and the recommended method for measuring and following tumor burden will be CT scan or MRI, to include the thorax, abdomen, and pelvis; the neck can be included if needed. Alternative modalities may be substituted for a CT scan at the discretion of the investigator, provided that the same modality is used throughout the study and the methodology is consist with RECIST v1.1.

For AML subjects, the International Working Group Response Criteria for Acute Myeloid Leukemia (Cheson et al 2003, Appendix D) will be used as the recommended method for measuring and following disease status. For MDS subjects, International Working Group Response Criteria for MDS (Cheson et al 2006, Appendix F) will be used as the recommended method for measuring and following disease status. For MF subjects, the proposed Response Criteria for MF (Tefferi et al 2013, Appendix G) will be used as the recommended method for measuring and following disease status.

The schedule for disease assessments will be at screening (this will be considered the baseline assessment) for all subjects and then once every 8 weeks throughout the study for solid tumor and once every 4 weeks for AML/MDS. The schedule for MF disease assessments will be at screening (this will be considered the baseline assessment), once every 4 weeks until Week 24, and once every 12 weeks after Week 24. For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease

status until the start of new anticancer therapy, documented disease progression, death, or end of study, whichever occurs first.

Bone marrow examination (aspirate and biopsy) is required at screening for subjects with diseases that are typically monitored through bone marrow examination, including AML, MDS, and MF. Note: subjects with a history of allogenic hematopoietic stem cell transplantation should have bone marrow collected and analyzed locally for the purposes of determining disease status (where applicable); however their sample does not need to be processed for sequencing due to chimeric potential.

Data from the pathology report result from the bone marrow examination will be captured in the eCRF. All bone marrow examinations should include a unilateral aspiration and biopsy with FISH and cytogenetic testing, when feasible and indicated. Subjects may be enrolled based on a biopsy only when a "packed marrow" precludes aspiration at the decision of the medical monitor. Results of assessments performed under standard of care before the signing of informed consent may be used as the baseline disease assessment in lieu of a study-specific procedure if performed within 60 days of the first dose of study drug (Cycle 1 Day 1) and if adequate archive material is available and there has been no anticancer therapy in the interim.

For disease assessment timepoints in AML, MDS, and MF that do not correspond to a bone marrow examination, peripheral blood myeloid blast percentage will be evaluated by microscopic evaluation or other appropriate methodology and will be used as appropriate in conjunction with other parameters (eg, cytopenias) in determining disease status.

For AML and MDS subjects, a bone marrow disease assessment is strongly encouraged during Cycle 2, preferably at Cycle 2 Day 1 for subjects who have a significant circulating blast count reduction (as determined by the investigator), including subjects who are not completely cleared of circulating blasts; a bone marrow biopsy and/or aspirates for response is to be performed at Cycle 4 Day 1 or earlier as clinically indicated, followed by every other month as clinically indicated, or upon circulating blood cell recovery to assess antileukemic activity (cytogenetic testing is not required if CR is not presented). Bone marrow examination schedule can be modified with approval from the medical monitor.

For MF subjects, bone marrow biopsy must be completed at screening or baseline visit, unless biopsy and data from previous 2 months are available. Additional biopsies will be performed at Week 24, Week 48, and every 24 weeks. If a biopsy is not possible or contraindicated, or the tissue requirement cannot be satisfied, this requirement may be waived with approval from the medical monitor.

For MF subject disease assessment with spleen palpation: spleen length will be assessed by manual palpation at every study visit (laboratory-only visits not included) and will be used for routine subject management. Investigators should use a soft centimeter ruler so that palpable spleen length is measured in centimeters and not in finger breadths. The edge of the spleen shall be determined by palpation and measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion. Spleen length must be recorded on the CRF.

[redacted]

7.8. Pharmacokinetic Assessments

7.8.1. Blood Sample Collection

Pharmacokinetic samples will be obtained at the visits indicated in the Schedule of Laboratory Assessments (Table 8) to evaluate plasma PK parameters as described in Appendix C. For PK sample collection, the following will be recorded:

- The exact date and time of the blood sample.
- The date and time of the last dose of study drug before blood collection (if applicable).
- The time of the most recent meal.

Subjects will receive reminder cards in advance of the study visit providing instructions to prepare for the visit (see Section 7.10.1). Instructions for plasma preparation and sample shipping will be provided in the Laboratory Manual.

7.8.1.1. Timed Pharmacokinetic Testing

Timed PK testing will be performed using the timepoints shown in Table 10. The timing of PK sample collection may be coordinated with other timed tests ([redacted] ECG). On these study dates, the subject should arrive at the research unit in the morning. If study drug has been previously dispensed, the reminder card (see Section 7.10.1) will remind the subject to refrain from taking the study drug at home that day. Subjects will also be reminded about fasting requirements, as applicable (see Table 10). A trough (predose) PK sample will be collected early in the study visit, followed by administration of the study drug and subsequent timed blood samples. The study drug will be administered with approximately 240 mL of water. Subjects should remain fasting from food or water for at least 1 hour postdose, after which a meal or snack may be consumed.

Adjustments to the timing of postdose blood collection may be made based on emerging PK[redacted] data, and additional sampling may be performed if emerging data suggest that drug exposure confirmation is required for subject safety; however, no more than 6 postdose timepoints will be used on a given day.

Table 10: Pharmacokinetic Sample Schedule

Visit	Predose	0.5 h ± 10 min	1 h ± 15 min	2 h ± 15 min	4 h ± 15 min	6 h ± 30 min
Cycle 1 Day 1[a]	X	X	X	X	X	X
Cycle 1 Day 8	X					
Cycle 1 Day 15 [a,b]	X	X	X	X	X	X
Cycle 1 Day 22	X					
Cycle 2 Day 1[a,c]	X	X	X	X	X	X

[a] No food intake 4 hours before dose and 1 hour after dose.
[b] In case of dose interruption, the new timing of PK sampling should be discussed with sponsor.
[c] Subjects in food-effect study only.

7.8.2. Urine Sample Collection

Urine will be collected from each subject at Cycle 1 Day 15 predose and then after administration of INCB059872. The predose sample should be kept separate from the rest of the samples collected. Total urine will be collected over a 6-hour interval after study drug administration. Urine containers should be kept at reduced temperature (refrigerated or ice bath) during collection. After the interval, urine should be mixed thoroughly. The total urine volume and the pH should be measured and recorded in the individual eCRF. Shipping and handling instructions will be provided in the Laboratory Manual; samples will be analyzed by the sponsor or its designee for parameters described in Appendix C.

7.8.3. Bioanalytical Methodology and Analysis

The plasma samples will be analyzed for INCB059872 by a validated liquid chromatography–tandem mass spectrometry assay. If there is sufficient urinary excretion of unchanged INCB059872 for assay, the urine samples will be assayed for INCB059872 by a validated assay. [redacted] Pharmacokinetic parameters that will be analyzed are shown in Appendix C, and the analysis methodology is described in Section 9.4.2.

7.8.4. Food-Effect Pharmacokinetic Testing

Pharmacokinetic testing for food effect on drug exposure will be performed on approximately 8 subjects enrolled in TG B1, Part 2; this will occur on Cycle 2 Day 1.

Subjects will have been fasted from food (not including water) for at least 4 hours. A standardized high-fat, high-calorie breakfast will be given to these subjects approximately 30 minutes before administration of study drug. Subjects must consume the entire breakfast within 25 minutes, and INCB059872 administration will begin 5 minutes after completing breakfast.

A high-fat, high-calorie meal (approximately 800-1000 calories, approximately 50% calories from fat) (FDA 2002) may consist of the following:

- 2 eggs fried in butter
- 2 strips of bacon
- 1 English muffin with butter
- 4 oz hash brown potatoes
- 8 oz whole milk

Alternative menus with the same caloric and fat content may be substituted with the prior approval of the study sponsor.

[redacted]

7.10. Other Study Procedures

7.10.1. Distribution of Subject Reminder Cards

Subjects will be provided with a reminder card at each visit. The subject reminder card will indicate the date/time of the next visit, and will also remind the subject that they should not take

their morning dose of study drug on Days 1, 8, 15, or 22 of Cycle 1 and then Days 1 and 15 for all other cycles, as they will take it after blood draws for safety evaluation have been completed. The reminder cards will have an area on which the date and time of the last dose taken (from the previous evening) and the time of their last meal before the visit should be recorded.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study 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 30 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 events(s) should be reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the Adverse Events form of the eCRF.

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 4. The CTCAE v4.03 severity of Grade 5 will not be used; AEs resulting in death will be graded accordingly using Grades 1 through 4 and have the outcome noted as fatal. If an event is not classified by CTCAE the severity of the AE will be graded according to the scale below to estimate the grade of severity:

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

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

- The severity grade (CTCAE Grade 1 to 4).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious AE (SAE) definition provided in Section 8.3.1.

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

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

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

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

8.2. Laboratory Test Abnormalities

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

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

8.3. Serious Adverse Events

8.3.1. Definitions

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

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied tumor type not associated with any deterioration in condition (ie, bone marrow biopsy for AML subjects)
  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the tumor type 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 one 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 30 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 30 days after the last dose of study drug should be reported to the sponsor it its designee only if the investigator suspects a causal relationship to the study drug.

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

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

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

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

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

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

- The study drug must be discontinued immediately (female subjects only; see Section 5.4.7 for the maximum permitted duration of study drug interruption).
- 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.

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

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

8.6. Warnings and Precautions

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

8.7. Data Monitoring Committee

No independent Data Monitoring Committee is planned for this study. Decisions to continue the enrollment in subsequent dose level cohort, dose level to be tested, as well as number of subjects to be evaluated, will be made after the appropriate data are collected and reviewed by sponsor representatives (eg, medical monitor) and investigators or designees. The group of sponsor representatives and investigators or designees will convene regularly (eg, once weekly) or ad hoc for specific discussions. Meeting minutes will be documented.

An internal Data Safety Monitoring Board (iDSMB) will review safety data at regular intervals throughout the study. The frequency of meetings will be contingent upon enrollment and availability of safety data for analysis and review. Details regarding membership, roles, and responsibilities of the committee are specified in the iDSMB charter.

8.8. Product Complaints

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

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

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

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

9. STATISTICS

9.1. Study Populations

The populations to be analyzed include the following:

- The full analysis set/safety population consists of subjects enrolled in the study who received at least 1 dose of study drug.
- The PK/[redacted] population consists of all enrolled subjects who had PK/[redacted] data.

9.2. Selection of Sample Size

Part 1 and Part 3 of the study will use a standard 3 + 3 dose-escalation design, and the sample size will depend on the frequency of DLTs and the number of dose-escalation cohorts before reaching the MTD. Approximately 3 to 6 subjects will be enrolled in each dose level. Using this design, the probability of dose escalation for various DLT rates is given in Table 11.

Table 11: Probability of Dose Escalation by DLT Rate

True DLT Rate	Probability of Dose Escalation
10%	90.6%
20%	70.9%
30%	49.4%
40%	30.9%
50%	17.2%
60%	8.2%

For Part 2, approximately 15 subjects will be enrolled for each expansion cohort. The evaluation of 15 subjects will provide a ≥ 90% chance of observing at least 1 toxicity with a true event rate of ≥ 15%.

For Part 4, for each of the combination cohorts (TG C1, TG D1, and TG E1), up to approximately 30 subjects will be enrolled. The evaluation of 30 subjects will provide approximately 90% chance of observing at least 1 toxicity with a true event rate of ≥ 7%.

9.3. Level of Significance

This is an exploratory study and no formal statistical tests will be performed. Unless otherwise specified, all confidence intervals will be at the 95% confidence level.

9.4. Statistical Analyses

All statistical analyses are exploratory in nature. Continuous variables will be summarized using means, medians, standard errors, minimums, and maximums. Categorical variables will be summarized using frequency counts and percentages.

9.4.1. Efficacy Analyses

For subjects with solid tumors, AML, and MDS, the proportion of subjects who meet the response criteria as appropriate for the tumor type will be summarized with descriptive statistics. [redacted].

For MF subjects, changes and percentage changes of spleen volume from baseline to Week 12 [redacted] will be summarized descriptively.

[redacted].

9.4.3. Safety Analyses

9.4.3.1. Adverse Events

A treatment-emergent AE 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 treatment-emergent AEs, 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. Severity of AEs will be based on the NCI CTCAE v4.03 using Grades 1 through 4.

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

9.4.3.2. 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 4 using CTCAE v4.03. The following summaries will be produced for the laboratory data:

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

9.4.3.3. 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 12), 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 12: 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

9.4.3.4. 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 13). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 13: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 470 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
RR	> 1330 ms	< 600 ms

QTcF = Fridericia correction.

9.4.3.5. Adverse Events of Special Interest

Based on preclinical data generated to date, there is reason to believe that subjects will develop some level of thrombocytopenia. No human data have been generated yet to support this. Additionally, there is a chance for a "rebound" effect on platelets (potentially thrombocytosis) once the drug is discontinued, but human data have not been generated to support this effect. Subjects will be monitored closely and based on CTCAE grading of thrombosis will be reported as AEs as appropriate.

9.4.4. Pharmacokinetic Analysis

The PK parameters of C_{max}, T_{max}, C_{min}, $AUC_{0\text{-}t}$, $t_{½}$, and Cl/F (INCB059872) will be calculated from the blood plasma concentrations of INCB059872 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. Refer to Appendix C 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. Analyses for the Data Monitoring Committee

Preplanned analyses of safety will be provided to the iDSMB at regular intervals throughout the study as specified in the iDSMB charter.

9.6. Interim Analysis

In Part 4, a stopping rule for futility is planned for each combination dose expansion treatment group. The futility analyses for combination TGs will be conducted when 15 subjects for each disease type have been treated and evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. The futility

analyses for TG D1 will be conducted when the first 15 subjects with AML or when the first 15 subjects with MDS have been treated. Combination TG C1 will be terminated for futility if ≤ 1 of the 15 subjects responded (ie, CR, CRi, MLFS) based on assessments provided by investigator. Combination TG D1 will terminate enrollment for subjects with AML if ≤ 2 of the first 15 AML subjects responded (ie, CR, CRi, MLFS) or will terminate enrollment for subjects with MDS if ≤ 2 of the first 15 MDS subjects responded (ie, CR or marrow CR), based on assessments provided by investigator. Combination TG E1 will be terminated for futility if ≤ 1 of the 15 subjects responded (ie, CR or PR) based on assessments provided by investigator.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

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

The investigator will be responsible for:

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

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

10.2. Accountability, Handling, and Disposal of Study Drug

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

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

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

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

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

10.3. Data Management

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

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

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

10.4. Data Privacy and Confidentiality of Study Records

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

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

10.5. Financial Disclosure

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

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

10.6. Publication Policy

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

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

Such methods include:

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

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

Source: CTFG 2014.

APPENDIX B. POTENT CYP2D6 INHIBITORS AND POTENT CYP3A4 INHIBITORS AND INDUCERS

In Vivo CYP2D6 Potent Inhibitor

Inhibitor	Therapeutic Class
Quinidine	antiarrhythmic
Fluoxetine	Antidepressants
Dacomitinib	Kinase inhibitors
Ecstasy	Recreational drug
Paroxetine	Antidepressant
Bupropion	Antidepressant

In Vivo CYP3A4 Potent Inhibitors

Inhibitor	Therapeutic Class
Indinavir/RIT)	Protease inhibitor
Tipranavir/RIT	Protease inhibitor
Ritonavir	Protease inhibitor
Cobicistat (GS-9350)	None
Indinavir	Protease inhibitor
Ketoconazole	Antifungal
Troleandomycin	Antibiotics
Telaprevir	Antivirals
Danoprevir/RIT	Antivirals
Elvitegravir/RIT	Treatments of AIDS
Saquinavir/RIT	Protease inhibitors
Lopinavir/RIT	Protease inhibitors
Itraconazole	Antifungals
Voriconazole	Antifungals
Mibefradil	Calcium channel blocker
LCL161	Cancer treatment

In Vivo CYP3A4 Potent Inhibitors (Continued)

Inhibitor	Therapeutic Class
Clarithromycin	Antibiotics
Posaconazole	Antifungals
Telithromycin	Antibiotics
Grapefruit juice DS	Food products
Conivaptan	Diuretics
Nefazodone	Antidepressants
Nelfinavir	Protease inhibitors
Saquinavir	Protease inhibitors
Idelalisib	Kinase inhibitors
Boceprevir	Antivirals

In Vivo CYP3A4 Potent Inducers

Inducers	Therapeutic Class
Rifampin	Antibiotics
Mitotane	Other antineoplastics
Avasimibe	Other antilipemics
Phenytoin	Anticonvulsants
Carbamazepine	Anticonvulsants
Enzalutamide	Antiandrogens
St John's Wort	Herbal medications
Rifabutin	Antibiotics
Phenobarbital	Anticonvulsants

Source: University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org.

APPENDIX C. PHARMACOKINETIC ANALYTICAL PARAMETERS

C_{ave}	Average steady-state plasma concentration (AUC_{0-12h}/12h or AUC_{0-24h}/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-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
$AUC_{0-\tau}$ (ie, AUC_{0-12h} or AUC_{0-24h})	Area under the steady-state plasma concentration-time curve over 1 dosing interval 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 ($[C_{max} – C_{min}]/C_{ave}$)

In addition, the following PK parameters may be calculated, whenever possible, for each subject based on the urine INCB059872 concentrations:

A_e	Amount of drug excreted in the urine over sampling interval
Cl_r	Renal clearance, where $Cl_r = A_e/AUC$
% Excreted or f_e	percent excreted in the urine, where % Excreted = 100 (A_e/dose)

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

APPENDIX D. INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR ACUTE MYELOID LEUKEMIA

Response Category	Response Definition
Complete remission (CR)[1]	Bone marrow blasts < 5 percent; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0×10^9/L (1000/μL); platelet count > 100×10^9/L (100,000/μL); independence of red cell transfusions
CR with incomplete recovery (CRi)	All CR criteria except for residual neutropenia (< 1.0×10^9/L [1000/μL]) or thrombocytopenia (< 100×10^9/L [100,000/μL])
Morphologic leukemia-free state	Bone marrow blasts < 5 percent; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5 to 25 percent; and decrease of pretreatment bone marrow blast percentage by at least 50 percent
Cytogenetic CR (CRC)	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)	No standard definition; depends on molecular target
Treatment failure	
Resistant disease (RD)	Failure to achieve CR or Cri or PR (Phase 1 trials); only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Relapse[2]	Bone marrow blasts ≥ 5 percent; or reappearance of blasts in the blood; or development of extramedullary disease

[1] All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

[2] In cases with low blast percentages (5 to 10 percent), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

Source: Cheson et al 2003.

APPENDIX E. EASTERN COOPERATIVE GROUP PERFORMANCE STATUS SCORING

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., 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.

APPENDIX F. INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR MYELODYSPLASTIC SYNDROME

Category	Response Criteria (Responses Must Be at Least 4 Weeks in Duration)
Complete remission (CR)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines Persistent dysplasia will be noted Peripheral blood: Hemoglobin (Hgb) ≥ 11 g/dL, Platelets ≥ 100×10^9/L, Neutrophils ≥ 1.0×10^9/L Blasts 0%
Partial remission (PR)	All CR criteria if abnormal before treatment, except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Treatment failure	Death during treatment Disease progression characterized by worsening of cytopenias, increase in % of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Disease progression (PD)	For patients with: - Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts - 5%-10% blasts: ≥ 50% increase in blasts to > 10% blasts - 10%-20% blasts: ≥ 50% increase in blasts to > 20% blasts - 20%-30% blasts: ≥ 50% increase in blasts to > 30% blasts Any of the following: - At least 50% decrement from maximum remission/response levels in granulocytes or platelets - Reduction in Hgb concentration by ≥ 2 g/dL - Transfusion dependence
Disease transformation	Transformation to AML (30% or more blasts)
Relapse after CR or PR	At least 1 of the following: - Return to pretreatment bone marrow blast % - Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets - Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
CYTOGENETIC RESPONSE	
Complete	Disappearance of the chromosomal abnormality without appearance of new ones
Partial	At least 50% reduction of the chromosomal abnormality
HEMATOLOGIC IMPROVEMENT (HI)	
Erythroid response (HI-E) (Pretreatment < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion evaluation
Platelet response (HI-P) (Pretreatment < 100×10^9/L)	Absolute increase of ≥ 30×10^9/L for patients starting with > 20×10^9/L Increase from < 20×10^9/L to > 20×10^9/L and by at least 100%
Neutrophil response (HI-N) (Pretreatment < 1.0×10^9/L)	At least 100% increase and an absolute increase of > 0.5×10^9/L

Source: Cheson et al 2006.

APPENDIX G. REVISED RESPONSE CRITERIA FOR MYELOFIBROSIS

Response Category	Required Criteria (for all categories, benefit must last for ≥ 12 weeks to qualify as a response)
Complete response	• Bone marrow:* Age-adjusted normocellularity; <5% blasts; ≤ Grade 1 MF† • Hemoglobin ≥ 100 g/L and < UNL; neutrophil count ≥ 1×10^9/L and < UNL; • Platelet count ≥ 100×10^9/L and < UNL; < 2% immature myeloid cells‡ • Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Partial response	• Hemoglobin ≥100 g/L and < UNL; neutrophil count ≥ 1×10^9/L and < UNL; platelet count ≥ 100×10^9/L and < UNL; < 2% immature myeloid cells‡ • Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH • Bone marrow:* Age-adjusted normocellularity; < 5% blasts; ≤ Grade 1 MF†, and peripheral blood: Hemoglobin ≥ 85 but < 100 g/L and < UNL; neutrophil count ≥ 1×10^9/L and < UNL; platelet count ≥ 50, but < 100×10^9/L and < UNL; < 2% immature myeloid cells‡ • Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Clinical improvement	• The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia§
Anemia response	• Transfusion-independent patients: a ≥ 20 g/L increase in hemoglobin level‖ • Transfusion-dependent patients: becoming transfusion-independent¶
Spleen response	• Baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable** or • Baseline splenomegaly that is palpable at > 10 cm, below the LCM, decreases by ≥ 50%** - Baseline splenomegaly that is palpable at < 5 cm, below the LCM, is not eligible for spleen response - Spleen response requires confirmation by MRI or computed tomography showing ≥ 35% spleen volume reduction.
Progressive disease‡‡	• Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or • ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm **or** • 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm or • Leukemic transformation confirmed by a bone marrow blast count of ≥ 20% or • Peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1×10^9/L that lasts for at least 2 weeks
Stable disease	• Belonging to none of the above listed response categories.
Relapse	• No longer meeting criteria for at least CI after achieving CR, PR, or CI, or • Loss of anemia response persisting for at least 1 month, or • Loss of spleen response persisting for at least 1 month.

See above for definitions of anemia response, spleen response, and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥ 20 g/L decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In addition, assignment to CI requires a minimum platelet count of ≥ $25{,}000 \times 10^9$/L and absolute neutrophil count of ≥ 0.5×10^9/L.

‖ Applicable only to patients with baseline hemoglobin of < 100 g/L. In patients not meeting the strict criteria for transfusion dependency at the time of study enrollment (see as follows), but who have received transfusions within the previous month, the pretransfusion hemoglobin level should be used as the baseline.

¶ Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of packed red blood cells (PRBC), in the 12 weeks before study enrollment, for a hemoglobin level of < 85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days before study enrollment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥ 85 g/L.

In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy.

** Spleen or liver responses must be confirmed by imaging studies where a ≥ 35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥ 35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.

‡‡ Progressive disease assignment for splenomegaly requires confirmation by MRI or computed tomography showing a ≥ 25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to posttreatment measurements.

Source: Tefferi et al 2013.

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

Note: Use as guidance in conjunction with institutional practice, the nivolumab package insert, and consultation with the medical monitor.

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

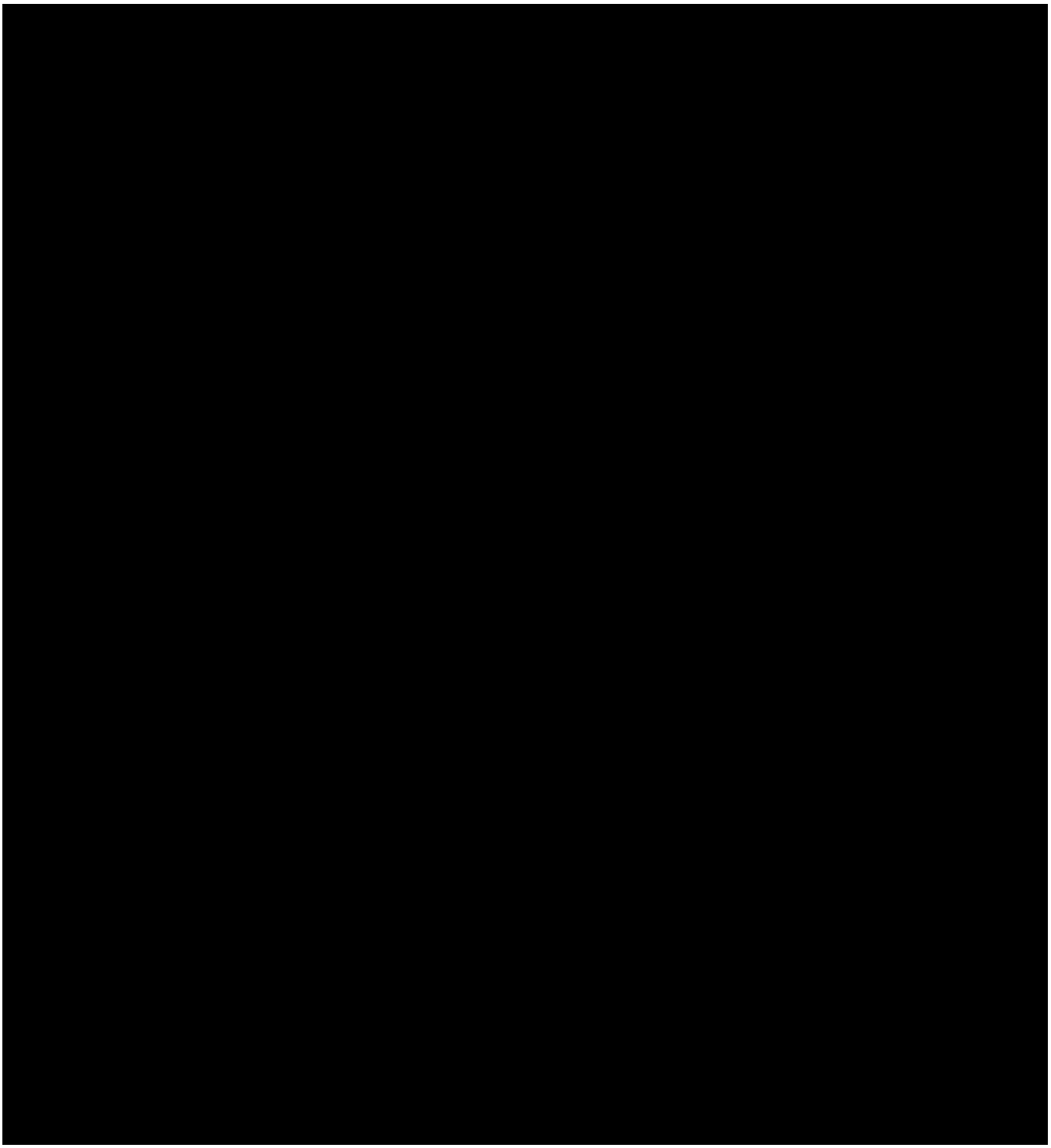
irAE	Supportive Care
Diarrhea/Colitis	***Note:*** Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). **For Grade 2 (mild to moderate new symptoms):** • Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. • Promptly start systemic steroids per institutional standard of care. • If event is not responsive within 3 to 5 days or worsens, gastrointestinal (GI) consult should be obtained for consideration of further work-up, and prompt treatment with IV methylprednisolone started. • If still no improvement within 3 to 5 days, consider starting immunosuppressives (eg, infliximab) after discussing with the medical monitor. ***Caution:*** Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Consult medical monitor if no resolution to ≤ Grade 1 in 3 to 4 days. • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]). **For Grade 3 or 4 (severe or new symptoms, new/worsening diarrhea, life-threatening):** • Treatment with systemic corticosteroids should be initiated per institutional standard of care. • Manage symptoms and consider GI consult for further work-up as appropriate. • If still no improvement within 3 to 5 days, consider starting immunosuppressives (eg, infliximab), after discussing with the medical monitor. ***Caution:*** Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN Guidelines for treatment of cancer-related infections [Category 2B recommendation]).

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

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

irAE	Supportive Care
Endocrinopathies	***Note:*** Subjects should be monitored for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Subjects may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated. **For Grade 2 (mild to moderate new symptoms):** • In hypophysitis, treat with systemic corticosteroids, per institutional standard of care. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered. ***Note: These suggested supportive care measures also apply to Grade 3 hypophysitis*** • In hyperthyroidism, nonselective beta-blockers (eg, propranolol) are suggested as initial therapy. • In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care. ***Note:*** Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. • Evaluate endocrine function and, as clinically indicated, consider pituitary scan. • For subjects with abnormal endocrine work-up, except for those with isolated hypothyroidism, consider short-term, high-dose corticosteroids (eg, methylprednisolone or IV equivalent) and initiate appropriate hormone replacement therapy. • For subjects with normal endocrine work-up (labs or MRI), repeat labs/MRI as clinically indicated. **For Grade 3 or 4 (severe or new symptoms, new/worsening endocrinopathies, life-threatening):** • Hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. • In hyperthyroidism, treat with an initial dose of IV corticosteroid followed by oral corticosteroids. Consider initiation of systemic corticosteroids at a dose of 1-2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy. Once improving, gradually taper immunosuppressive steroids over ≥ 4 weeks. • In hypophysitis, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered. • For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity. • Consult endocrinologist. • Consult medical monitor.

irAE	Supportive Care
Neuropathies	***Note:*** Monitor subjects for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. **For Grade 2 (mild to moderate new symptoms):** • Consider systemic corticosteroids per institutional standard of care in addition to appropriate symptomatic treatment. • If no improvement within 3-5 days, consider additional work-up and consider treating with additional immunosuppressive therapy (eg, IV IgG), after discussing with the medical monitor. **For Grade 3 or 4 (severe or new symptoms, new/worsening neuropathies, life-threatening):** • Consider initiation of systemic corticosteroids (IV administration should be strongly considered) for severe neuropathies. • Institute medical intervention as appropriate for management of severe neuropathy. • If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and consider treating with additional immunosuppressants (eg, IV IgG) after discussing with the medical monitor. • Once stable, gradually taper steroids over ≥ 4 weeks.



APPENDIX K. PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment (Version) 1:	19 JAN 2016
Amendment (Version) 2:	28 JUL 2016
Amendment (Version) 3:	22 SEP 2017
Amendment (Version) 4:	06 NOV 2017
Amendment (Version) 5:	30 JUL 2018
Amendment (Version) 6:	19 APR 2019
Amendment (Version) 7:	13 JUN 2019
Amendment (Version) 8:	15 JUN 2020

Amendment 8 (15 JUN 2020)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to add a principal coordinating investigator [redacted]

1. **Synopsis**

   Description of change: Updated to add Dr. [redacted], MD as the principal coordinating investigator for the study.

   Rationale for change: To identify the principal coordinating investigator for the study.

2. **Synopsis; [redacted]; Section 5.5.1, Withdrawal Criteria; Section 6, Study Assessments (Table 7: Schedule of Assessments); Section 6.4.1, Safety Follow-Up; Section 6.4.3, Survival Follow-Up; Section 7.10.2, Data Collection For Survival Follow-Up; Section 9.4.1, Efficacy Analyses**

   Description of change: Sections 6.4.3 and 7.10.2 were removed and all other applicable text was updated to remove survival follow-up [redacted] from the study.

   [redacted]

Amendment 7 (13 JUN 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to include additional safety monitoring and modify the inclusion criteria for MDS patients in Treatment Group D for Parts 3 and 4 of the Protocol.

1. **Synopsis; Section 3.1, Subject Inclusion Criteria; Section 4.1.3, Combination Dose-Finding (Part 3); Section 4.1.4, Combination Dose Expansion (Part 4) (including Figure 1: Study Design)**

   Description of change: All applicable sections have been updated to modify the inclusion criteria for MDS subjects in Treatment Group D for Parts 3 and 4 of the Protocol.

   Rationale for change: Per FDA request.

2. **Synopsis; Section 6, Study Assessments (Table 8: Schedule of Laboratory Assessments)**

   Description of change: Two additional collections for hematology were added in the first 2 weeks of study treatment, one at Cycle 1 Day 4 and another at Cycle 1 Day 11.

   Rationale for change: To include additional hematology monitoring to the study in response to platelet changes with INCB059872.

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 6 (16 APR 2019)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update Treatment Group D to include MDS subjects, update dose interruption and modification guidance, update inclusion criteria, and update the schedule of assessments for MF subjects. This amendment includes the changes to Protocol INCB 59872-101 Amendment 5 (30 JUL 2018) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 2.2.2, Secondary Endpoints; [redacted]; Section 3.1, Subject Inclusion Criteria; Section 4.1.3, Combination Dose-Finding (Part 3); Section 4.1.4, Combination Dose-Expansion (Figure 1, Study Design); Section 9.6, Interim Analysis**

   Description of change: All applicable sections have been updated to include MDS subjects eligible to receive azacitidine as first-line therapy in Treatment Group D for Parts 3 and 4 of the Protocol.

   Rationale for change: The scientific rationale that was applicable to AML is also applicable for MDS patients.

2. **Synopsis; Section 4.1.4, Combination Dose Expansion (Part 4); Section 9.6, Interim Analysis**

   Description of change: Futility analysis was updated to include MLFS in the AML interim analysis.

   Rationale for change: Revised to include subjects who are having a response in the absence of platelet recovery due to on-target activity of LSD1 inhibition.

3. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Exclusion Criterion #7 was updated to allow subjects to enroll in the study with a QTc interval of up to 470 milliseconds.

   Rationale for change: Updated as a more appropriate criterion in this patient population.

4. **Section 5.4.1, Dose Modification of INCB059872**

   Description of change: Updated dose modification guidance for INCB059872 to permit subjects in Treatment Groups C and D having a bone marrow blast response to explore a less intensive dosing regimen.

   Rationale for change: Updated to allow for platelet recovery in subjects demonstrating a bone marrow blast response that may not otherwise occur on the recommended dosing regimen due to the activity of INCB059872.

5. **Section 5.4.7, Criteria and Procedures for Dose Interruptions and Adjustments of INCB059872 (Table 5: Guidelines for Interruption and Restarting of Study Drug)**

   Description of change: Table 5 was updated to provide additional guidance and clarification regarding the guidance for interruption and restarting INCB059872 for thrombocytopenia in AML/MDS/MF.

Rationale for change: To provide additional guidance regarding platelet changes in the AML/MDS/MF patient population.

6. **Section 6, Study Assessments (Table 7: Schedule of Assessments); Section 7.6, Efficacy Assessments; [redacted] Section 7.5.5, Laboratory Assessments**

   Description of change: Table 7 was updated to reduce the frequency of disease assessments for MF subjects after treatment Week 24. [redacted]. Language was added to allow for decreased visits after Week 24 with medical monitor approval for MF subjects

   Rationale for change: Updated with investigator feedback regarding the standard of care in the clinic for this patient population.

7. **Section 5.6.1, Restricted Medications; Section 5.6.2, Prohibited Medications**

   Description of change: Updated to prohibit the use of hydroxyurea within the 48 hours before initiation of study treatment and 24 hours before collection of [redacted] and to allow the use of hydroxyurea on treatment to treat hyperleukocytosis with medical monitor approval.

   Rationale for change: Updated with investigator feedback regarding the standard of care in the clinic for this patient population.

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 5 (30 JUL 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update and add treatment modification guidance for SAEs with suspected causal relationship to study drug. This amendment includes the changes to Protocol INCB 59872-101 Amendment 4 (06 NOV 2017) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Section 5.4.7, Criteria and Procedures for Dose Interruptions and Adjustments of INCB059872 (Table 5: Guidelines for Interruption and Restarting of Study Drug)**

   Description of change: Table 5 was updated to include additional guidance for treatment modification or discontinuation with decreases in platelets or leukocytosis.

   Rationale for change: To provide additional guidance for dose modifications and ensure patient safety, to the extent possible, in this difficult population.

2. **Synopsis; Section 8.7, Data Monitoring Committee; Section 9.5, Analyses for the Data Monitoring Committee**

   Description of change: All relevant sections were updated to iDSMB from SMC.

   Rationale for change: To provide consistency with the internal name given to the safety monitoring board implemented in this study.

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 4 (06 NOV 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update the selected doses for monotherapy expansion in Part 2, update the starting doses of INCB059872 in Part 3, clarify DLT evaluability criteria, add early stopping rules for futility in Part 4, adjust the endpoints, revise the eligibility criteria for Cohorts D and D1, add an internal safety committee, and remove references to a pharmacologically active dose. This amendment includes the changes to Protocol INCB 59872-101 Amendment 3 (22 SEP 2017) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 4.1.2, Monotherapy Dose Expansion (Part 2); Section 4.1.3, Combination Dose-Finding (Part 3)**

   Description of change: The selected doses for monotherapy expansion in Part 2 were included to specify that expansion cohort TG A1 would be at INCB059872 4 mg QD and monotherapy dose expansion cohorts TG A2, TG B1, and TG B2 would be at INCB059872 3 mg QOD. The selected starting does for combination dose-finding (Part 3) were included to specify that Combination TG C and TG D would start at INCB059872 2 mg QD in combination with either ATRA or azacitidine and that TG E would start at INCB059872 3 mg QOD in combination with nivolumab. All relevant Protocol sections were revised accordingly.

   Rationale for change: Per FDA recommendation.

2. **Synopsis; Section 4.1.1, Monotherapy Dose Escalation (Part 1); Section 4.1.3, Combination Dose-Finding (Part 3); Section 4.3.2, Replacement of Subjects**

   Description of change: Revised to clarify that if a subject does not complete the minimum number of doses and still has a DLT, the DLT will be counted in the numerator for the purposes of dose escalation decisions. All relevant Protocol sections were revised accordingly.

   Rationale for change: Per FDA recommendation.

3. **Synopsis; Section 4.1.4, Combination Dose Expansion (Part 4); Section 9.6, Interim Analysis**

   Description of change: Revised to include interim futility analysis for each of the treatment groups in Part 4.

   Rationale for change: Per FDA recommendation.

4. **Synopsis; Section 2, Study Objectives and Endpoints**

   Description of change: Objectives were revised to include determination of recommend dose for further study in Part 3. For Parts 2 (monotherapy dose expansion) and 4 (combination dose expansion), the primary objective was revised to assess safety and tolerability, the objective of preliminary antitumor activity was changed to a secondary objective, [redacted]. All corresponding endpoints and relevant Protocol sections were revised accordingly.

Rationale for change: Per FDA recommendation.

5. **Synopsis; Section 3.1 Subject Inclusion Criteria; Section 4.1.3, Combination Dose-Finding (Part 3); Section 4.1.4, Combination Dose Expansion (Part 4; Figure 1, Study Design); Section 11, References**

   Description of change: The eligibility criteria for Treatment Groups D/D1 were revised using the Ferrara et al 2013 criteria to more objectively describe the intended patient population. Inclusion Criterion #4 was revised to specify "newly-diagnosed treatment-naive AML patients who are unfit to tolerate standard intensive chemotherapy at study entry." All relevant Protocol sections were revised accordingly.

   Rationale for change: Per FDA recommendation.

6. **Synopsis; Section 8.7, Data Monitoring Committee; Section 9.5, Analyses for the Data Monitoring Committee**

   Description of change: Section 8.7 was revised to include an internal Study Monitoring Committee to review safety data at regular intervals throughout the study to monitor for any increase in risk to study subjects. All relevant Protocol sections were revised accordingly.

   Rationale: Per FDA recommendation.

7. **Synopsis; Section 1.6.2, Clinical Experience With INCB059872; Section 4.1, Overall Study Design; Section 4.1.1, Monotherapy Dose Escalation (Part 1); Section 4.1.2, Monotherapy Dose Expansion (Part 2); Section 4.1.3, Combination Dose-Finding (Part 3); Section 5.4.10, Criteria for Permanent Discontinuation of INCB059872**

   Description of change: Removal of reference to a PAD from the Protocol, as the recommended monotherapy dose of INCB059872 has been selected based on tolerability and not pharmacologic activity, and identification of a PAD is not listed as an endpoint.

   Rationale: Per FDA recommendation.

8. **Synopsis; Section 4.3.1, Planned Number of Subjects**

   Description of change: This section was updated to change the planned number of number to 215.

   Rationale: To provide a more accurate estimation of the number of planned subjects.

[redacted]

Amendment 3 (22 SEP 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to add dose-finding and expansion cohorts to evaluate INCB059872 in combination with select conventional care treatment regimens in subjects with select advanced malignancies and to update aspects of the monotherapy design based on emerging data from the current study. This amendment includes the changes to Protocol INCB 59872-101 Amendment 2 (28 JUL 2016) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 1, Introduction; Section 2, Study Objectives and Endpoints; Section 3, Subject Eligibility; Section 4, Investigational Plan; Section 5, Treatment; Section 6, Study Assessments; Section 9, Statistics; Appendix H, Procedures and Supportive Care Guidelines for Subjects Exhibiting Immune-Related Adverse Events**

   Description of change: The study design was revised to include conventional care combination dose-finding and expansion cohorts. All relevant Protocol sections, including tables and figures, were revised accordingly.

   Rationale for change: To provide the background, rationale, study design, study objectives/endpoints, inclusion/exclusion criteria, treatment details, study assessments, and statistical considerations in order to research INCB059872 in combination with conventional care regimens in select advanced malignancies.

2. **Synopsis; Section 2, Study Objectives and Endpoints; Section 6, Study Assessments; Section 7, Conduct of Study Assessments and Procedures;** [redacted]

   Description of change: Endpoints updated, Schedule of Assessment updated, and appendices added for efficacy evaluation in myelofibrosis.

   Rationale for change: To provide more disease-specific detail to response determination and efficacy measures for select advanced malignancies.

3. **Title Page**

   Description of change: Added EudraCT number.

   Rationale for change: To provide the EudraCT number.

4. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Exclusion Criterion #4 was revised to provide clarification, and Exclusion Criterion #5a was revised to indicate that subjects can be included in the study if total bilirubin is $\leq 1.5 \times$ upper limit of normal (ULN) if there is no liver metastases or $\leq 3 \times$ ULN in the presence of liver metastases or if bilirubin increase was due to presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia).

Rationale for change: To provide additional clarification of the population requiring medical monitor approval for values below the lower limits in select laboratory values and to provide appropriate requirements for subjects with liver metastases.

5. **Synopsis; Section 5, Treatment**

   Description of change: Addition of text to specify the number of doses and guidance missed doses within a cycle using the once daily (QD) schedule.

   Rationale for change: To provide clarification for dosing in the QD schedule.

6. **Section 1.6.2, Clinical Experience With INCB059872**

   Description of change: This section was updated to include a preliminary, unaudited summary of safety data from the INCB 59872-101 study inclusive of the monotherapy dose cohorts initial evaluation period for the proposed INCB59872 starting doses in the added combination cohorts.

   Rationale: To provide an updated summary of the adverse event data observed in this study.

7. **Section 5.1.1, Subject Numbering and Treatment Assignment**

   Description of change: Addition of text to include that sites will have to contact the Interactive Response Technology (IRT) at the time of subject enrollment to receive a subject number and to update the IRT system at each visit to receive the treatment allocation.

   Rationale: To provide clarification of IRT procedures.

8. **Section 5.6, Concomitant Medications**

   Description of change: This section was updated to include additional information for recording concomitant medications in the electronic case report form.

   Rationale: To provide clarification for recording concomitant medications.

9. **Synopsis; Table 7, Schedule of Assessments**

   Description of change: This section was updated to include a timeframe for computed tomography or magnetic resonance imaging assessments for solid tumors and to adjust the timeframe for Cycle 2 Day 1 assessments.

   Rationale: To provide clarification and flexibility for efficacy assessments in solid tumors and to provide consistency for the time window for scheduled visits.

10. **Synopsis; Section 8.7, Data Monitoring Committee**

    Description of change: This section was updated to provide details for the safety and data meetings occurring throughout the study.

    Rationale: To provide clarification of the attendees and meetings, which will occur throughout the study, regarding dose escalation, safety, etc.

11. **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 (28 JUL 2016)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update the language in the inclusion and exclusion criteria to provide more clarity, to provide additional language regarding different regimens to be explored in this study, and to update Tables 1 through 5.

The changes made to the Protocol INCB 59872-101 Amendment 1 (19 JAN 2016) are summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 3.1, Subject Inclusion Criteria**

   Description of change: In inclusion criterion #5, the number of slides from biopsy has been changed from 25 unstained slides (with a minimum of 15) to approximately 15 slides.

   Rationale for change: This will allow more flexibility in what sites will be able to provide.

2. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   a. **Description of changes:** Language added at the end of exclusion criterion #5: "Laboratory and medical history parameters outside Protocol-defined range *unless associated with primary malignancy or metastatic disease and with medical monitor approval*."

      Rationale for change: To not exclude subjects with laboratory abnormalities due to malignancy.

   b. **Description of change:** Exclusion criterion #8 was revised to indicate that subjects must have recovered from all radiation-related toxicities, *including radiation pneumonitis* (instead of requiring that subjects have not had radiation pneumonitis).

      Rationale for change: The exclusion criterion was reworded to be clear that the radiation pneumonitis was associated with the last radiation therapy.

   c. **Description of change:** Exclusion criterion #11 has been split into 2 criteria: #11 is now "History of human immunodeficiency virus infection" and #23 is "Evidence of active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection."

      Rationale for change: To provide clarity to the different issues that need to be regarded for exclusion; to provide a simple definition for hepatitis B and hepatitis C exclusion criteria.

   d. **Description of change:** A temporal condition has been added to exclusion criterion #13: "History of clinically significant or uncontrolled cardiac disease, *including recent history (within 6 months)* of unstable angina, acute myocardial infarction, New York Heart Association Class III or IV congestive heart failure, or arrhythmia requiring therapy."

      Rationale for change: To ensure that subjects are not entering study with an unstable cardiac condition.

3. **Section 4.1, Overall Study Design**

   Description of change: Language has been added to clarify the option to explore a different dosing regimen and how the dose will be selected: "Subjects will receive INCB059872 doses once QOD on a 28-day continuous therapy schedule; *if QOD is well tolerated, the next dose may be administered at a different dosing regimen (ie, QD) but will not exceed the 100% dose escalation for a total daily dose*."

   Rationale for change: To provide more clarity to steps for dose increase/regimen adjustment.

4. **Section 5.4.2, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose of INCB059872 (Table 1: Definition of Dose Limiting Toxicity)**

   Description of change: Conditions for febrile neutropenia were changed from "all tumor types" to "for solid tumors only."

   Rationale for change: Febrile neutropenia is not a relevant dose-limiting toxicity for hematologic malignancies.

5. **Section 5.4.6, Criteria and Procedures for Dose Interruptions and Adjustments of INCB059872 (Table 2: Guidelines for Interruption and Restarting of Study Drug)**

   Description of change: Parameters for ALT and AST have been changed to allow up to 20 × the upper limit of normal before discontinuation.

   Rationale for change: More flexibility is required based on tumor types and disease process.

6. **Synopsis**

   Description of change: Under Study Schedule/Procedures, the following sentence was deleted from the "Laboratory tests for safety" section: "Subjects with AML/MDS/MF will have bone marrow aspirate/biopsy evaluations and laboratory assessments as part of the disease response assessment performed." In the "Clinical assessments" section, the list of examples for assessment of disease status at screening was revised to include bone marrow *biopsy*/aspirate and *peripheral blood*.

   Rationale for change: Tables 3 and 4 were modified to provide more clarity to the procedures required and the tissue required for the analysis at the different timepoints.

7. **Section 5.8.4, Criteria and Procedures for Dose Increases of INCB059872**

   Description of change: The fourth bullet was revised to indicate "The subject is willing to submit to the PK sampling and safety monitoring schedules as in Cycle 1 ***Day 15***."

   Rationale for change: This language was added to ensure it was clear that subjects whose dose of study is increase must allow additional pharmacokinetic and safety monitoring that is outlined in Cycle 1 Day 15.

8. **Section 6, Study Assessments (Table 3: Schedule of Assessments; Table 4: Schedule of Laboratory Assessments; Table 5: Local Laboratory Tests: Required Analytes)**

   Description of change: Modifications were made to Tables 3 through 5 to clarify clinical and laboratory assessment schedules and ensure correlation with the body text of the Protocol.

   Rationale for change: The tables were updated for clarity and better instruction for the clinical sites.

9. **Section 7.5.4, Electrocardiograms**

   Description of change: More detail added regarding the timing for single electrocardiograms (ECGs) and triplicate ECGs.

   Rationale for change: To clarify the ECG procedures and make the text consistent with the Schedule of Assessments (Table 4).

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, including changes noted in Protocol Administrative Change 1 (dated 08 MAR 2016): deleting the safety laboratory line item and adding the survival follow-up visit in Table 3; adding lipid panel to Table 4; and adding blood urea nitrogen to Table 5.

Amendment 1 (19 JAN 2016)

Overall Rationale for the Amendment:

The primary purpose of Amendment 1 is to delete combination therapy from the study design, refine exclusion criteria, add to the prohibited medication list, increase dose-limiting toxicity language, improve language for restarting study drug and at what increments, and add stopping rules.

The changes made to the Protocol INCB 59872-101 (15 DEC 2015) are summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 1, Introduction; Section 2, Study Objectives and Endpoints; Section 3, Subject Eligibility; Section 4, Investigational Plan; Section 5, Treatment; Section 6, Study Assessments; Section 7.7.4, Food-Effect PK Testing; Section 8.3.2, Reporting; Section 9.2, Selection of Sample Size; Section 11, References**

   Description of change: All references to combination treatment have been removed. The study design has changed to include only Part 1 (dose escalation) and Part 2 (dose expansion). The additional treatment groups and parts associated with combination therapy have been removed. The number of subjects has been updated accordingly (total number of subjects is now 108 instead of 230). Additionally, the background, risk, and dosing information on the 3 combination therapies have been removed. In Section 11, references supporting the combination and product inserts for the combination products have been deleted. Figure 1 (Study Design) has been updated, and Table 3 (Schedule of Assessments) has been updated to delete the administration of the combination products.

   Rationale for change: Per FDA request.

2. **Synopsis; Section 3, Study Population**

   Description of change: The study population language has been refined to read, "Subjects with advanced or metastatic malignancies who are ineligible for all therapeutic options that are standard of care or known to confer benefit, or who refuse these treatments."

   Rationale for change: Per FDA request. Language was provided by Agency.

3. **Synopsis; Section 4.1, Overall Study Design**

   Description of change: The following language was added: "Dose escalation should proceed in smaller increments (ie, by no more than 50%) if a DLT is observed, or if 2 or more subjects at a given dose level experience Grade 2 or higher AEs (unless they are clearly and incontrovertibly due to an alternative cause)."

   Rationale for change: Per FDA request. Language was provided by Agency.

4. **Table 1: Definition of Dose-Limiting Toxicity**

   Description of change: Delete "Other events considered no clinical significant in the judgment of the investigator" from nonhematologic toxicity.

   Rationale for change: Per FDA request.

5. **Section 5.4.2, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose of INCB059872**

   Description of change: In Table 1 (Definition of Dose-Limiting Toxicity), the definition of DLT was refined for thrombocytopenia, both for solid tumors and for AML/MDS/MF.

   Rationale for change: Per FDA request.

6. **Section 5.4.6, Criteria and Procedures for Dose Interruptions and Adjustments of INCB059872**

   Description of change: Table 2 (Guidelines for Interruption and Restarting of Study Drug) was revised to include discontinuation rules for Grade 4 events (asymptomatic versus symptomatic) and interruption and restarting rules for Grade 3 events. This was applied throughout the table. Language was also added to the table to clarify that granulocyte colony-stimulating factor is allowed in the management of neutropenia for low ANC in solid tumors.

   Rationale for change: Per FDA request.

7. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Revised Exclusion Criterion #5 to include total bilirubin levels only.

   Rationale for change: Per FDA request.

8. **Synopsis; Section 4.1, Overall Study Design**

   Description of change: Addition of stopping rules: "If ≥ 5 subjects in the first 15 subjects of any cohort, cumulatively (or more than 33% of subjects in cohorts larger than 15 subjects) experience DLTs during Cycle 1, then further enrollment to the cohort will be stopped, and a lower dose level may be explored."

   Rationale for change: Per FDA request.

9. **Synopsis; Section 3.2, Subject Exclusion Criteria; Section 5.6, Concomitant Medications; Appendix B, Potent CYP2D6 Inhibitors and Potent CYP3A4 Inhibitors and Inducers**

   Description of change: Changed language to prohibit use of potent CYP2D6 inhibitors and potent CYP3A4 inducers and inhibitors. Refined the tables in Appendix B to include only lists of potent CYP2D6 inhibitors and potent CYP3A4 inhibitors and inducers.

   Rationale for change: Per FDA request.

[redacted]

[redacted]