Clinical Study Protocol

INCB 52793-101 / NCT02265510

A Phase 1/2 Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB052793 in Subjects With Advanced Malignancies

Product:	**INCB052793 in combination with INCB050465 and standard of care, and itacitinib (INCB039110) in combination with azacitidine**
IND Number:	**134,089**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Date of Protocol:	**01 MAY 2014**
Date of Amendment 1:	**09 JUN 2014**
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Date of Amendment 7:	**27 FEB 2017**
Date of Amendment 8:	**31 MAR 2017**
Date of Amendment 9:	**02 MAY 2017**

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

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for INCB052793. I have read the INCB 52793-101 Protocol Amendment 9 (dated 02 MAY 2017) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: INCB052793 and in combination with INCB050465, itacitinib (INCB039110)

Title of Study: A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB052793 in Subjects With Advanced Malignancies

Protocol Number: INCB 52793-101	**Study Phase:** 1/2

Primary Objectives:

- Phase 1a: To assess the safety and tolerability of INCB052793 in subjects with advanced malignancies and select doses for further evaluation.
- Phase 1b: To assess the safety and tolerability of INCB052793 in combination with standard therapies and the novel phosphatidylinositol 3-kinase δ (PI3Kδ) inhibitor INCB050465 in subjects with advanced malignancies.
- Phase 2: To evaluate the efficacy of INCB052793 in combination with azacitidine and of itacitinib in combination with azacitidine in subjects with acute myeloid leukemia (AML) and high-risk myelodysplastic syndromes (MDS) who have failed prior therapy with hypomethylating agents (HMA), based on overall response rate (ORR).

Secondary Objectives:

- To assess preliminary efficacy by assessing the ORR in subjects with advanced malignancies.
- To assess the safety and tolerability of INCB052793 in combination in azacitidine and of itacitinib in combination with azacitidine in subjects with AML and high-risk MDS who have failed prior therapy with HMA.
- To assess the pharmacokinetics (PK) of INCB052793 as monotherapy administered in the fasted state and the effect of food on the PK of INCB052793.
- To assess the PK of INCB052793 when administered in combination with standard therapies and INCB050465 in subjects with advanced malignancies, to assess the PK of INCB050465 when administered in combination with INCB052793, and to asses the PK of itacitinib when administered in combination with azacitidine.

[redacted]

Overall Study Design:

The study will be conducted in 2 phases (Phase 1a/1b and Phase 2). Phase 1a will be conducted with INCB052793 monotherapy dose escalation (Part 1) and dose expansion (Part 2). Phase 1b will comprise treatment cohorts in which INCB052793 will be administered in combination with gemcitabine and *nab*-paclitaxel in select solid tumors (Cohort A); dexamethasone, carfilzomib, bortezomib, lenalidomide, and pomalidomide/dexamethasone in subjects with multiple myeloma (MM; Cohorts B, C, D, E, and G, respectively); azacitidine in subjects with AML or MDS (Cohort F), and INCB050465 in subjects with lymphomas (Cohort H), each including both a dose escalation (Part 1) and an optional dose expansion (Part 2). Phase 2 will include 2 treatment cohorts in which subjects with AML and high-risk MDS who failed prior therapy with HMA will receive azacitidine in combination with INCB052793 (Cohort I) or in combination with itacitinib (Cohort J).

Phase 1a Monotherapy:

Phase 1a will include Part 1 dose escalation starting with 25 mg once daily (QD) to determine the maximum tolerated dose (MTD) and/or pharmacologically active dose (PAD) of single-agent INCB052793 in 2 treatment groups (A and B). This dose will be chosen for further evaluation. Part 2 dose expansion will evaluate the chosen dose as monotherapy.

Part 1 Dose Escalation: The dose escalation will start with Treatment Group A (TGA; advanced or metastatic solid tumors) at 25 mg QD and consist of a 21-day cycle, with Cycle 1 Day 1 as the first day of treatment. Open-label dose escalation will consist of an initial cohort using a 3 + 3 design with dose doubling until either Grade 2 or greater toxicities or unbound AUC at steady state exceeds the value (25.3 μM·h) corresponding to the no-observed-adverse-effects level (NOAEL) in the most sensitive species evaluated in GLP toxicology studies (rat at 15 mg/kg). Each dose level will be observed for a period of 21 days before enrolling the next cohort and administering the next dose level. Treatment Group B (TGB; advanced hematologic malignancies) will follow the same dose-escalation design, beginning enrollment at the PAD when it is determined.

Subjects who receive at least 17 of 21 days (or ≥ 80%) of fasted study drug at the level assigned to that cohort, or who experience a dose-limiting toxicity (DLT), will be considered evaluable for determining tolerability of dose. Subjects enrolling but not meeting these criteria may be replaced in order to fill the cohort.

The starting dose of INCB052793 (25 mg QD in TGA; PAD in TGB) will be escalated if 0 of the first 3 evaluable subjects enrolled experience a DLT. Increases to study drug will be up to 100% (ie, 25 mg, 50 mg, 100 mg, and 150 mg) if there are no reported Grade 2 or greater toxicities and no subject has an unbound AUC at steady state that exceeds 25.3 μM·h. Otherwise, increases of study drug dose will be limited to no more than 50% in successive cohorts, using QD regimen (ie, 25 mg, 35 mg, 50 mg, 75 mg, 100 mg, and 150 mg). If no DLTs are observed in the initial 3 subjects, the next cohort will begin enrollment. If 1 DLT is observed in the first 3 subjects, 3 additional subjects will be enrolled in the cohort. If a DLT occurs in one-third or more of the total cohort (≥ 2 of 3 or 6), then the MTD will be deemed to have been exceeded, and the next lower dose level will be deemed to be the MTD. If the dose-escalation increment has been 100%, then an intermediate lower dose level may be explored. Thus, the MTD will be defined as 1 dose level below that at which one-third or more of subjects in a particular cohort experience DLTs. Dose-limiting toxicities occurring during the first 21 days of treatment will guide dose escalation and determination of the MTD; however, subjects who may have not experienced a DLT but who experienced intolerable, lower grade persistent toxicity determined to be due to study drug will be considered in the determination of the study drug dose in the expansion cohorts. Only toxicities with a clear alternative explanation (ie, due to disease progression, comorbid condition, concomitant medication) can be deemed a non-DLT for determination of the PAD/MTD.

Part 2 Dose Expansion: The expansion may proceed with a PAD, the MTD or the highest dose tested if the MTD is not reached:

- TGA (advanced or metastatic solid tumors) and TGB (advanced hematologic malignancies) of approximately 12 subjects each in 1 or 2 expansion dose levels (PAD and/or MTD or highest dose tested if MTD is not reached for each group) will be treated with the selected doses of INCB052793 as a single agent to further determine safety, tolerability, efficacy, PK, [redacted] in this population.
- For both TGA and TGB, a study of the effect of food on the PK of INCB052793 will be conducted on this expanded cohort. Results from the food-effect study will dictate whether study drug will be administered to subjects in the fasted or fed state in ongoing subjects in Phase 1a and Phase 1b.

Phase 1b Combination Therapy:

Phase 1b will comprise treatment cohorts evaluating INCB052793 when administered in combination with standard therapies for select solid tumors (Cohort A), MM (Cohorts B, C, D, E and G), AML/MDS (Cohort F) and with the PI3Kδ inhibitor INCB050465 in lymphoma (Cohort H). Each treatment cohort will include 2 parts. Part 1 is a 3 + 3 dose escalation that will evaluate increasing doses of INCB052793

in combination with standard-of-care agents and INCB050465 in select solid tumors and select advanced hematological malignancies. Part 2 will be an optional expansion to further evaluate the safety and preliminary efficacy of the combination at the selected INCB052973 dose. Timing for the initiation of Phase 1b enrollment will be determined by the sponsor based on the available safety/tolerability and PK/[redacted] data from Phase 1a. The sponsor may elect to open certain Phase 1b treatment cohorts before others or to not open specific cohorts.

Enrollment into Cohorts A, C, D, E, G and H will not be conducted as per Amendment 7 of the Protocol.

Part 1 Dose Escalation: The starting dose of INCB052793 in each treatment cohort will be designated as Dose Level 1. Dose Level 1 will be 50% to 100% of the PAD (maximum of 75% of MTD) in Phase 1a (rounded down to the next lowest dose based on available tablet strengths). Dose escalation will proceed using a 3 + 3 design. Each cohort will be observed for a minimum of 1 cycle before the next cohort begins enrollment. Within each cohort, subjects will be considered nonevaluable for safety and replaced if they have received < 75% of the planned doses of study drug or standard therapy during the first cycle of treatment and they have not experienced a DLT. If Dose Level 1 is deemed tolerable, the INCB052793 dose in the respective combination therapy may be escalated to Dose Level 2, which will be ≤ 50% higher than Dose Level 1. Additional dose levels may be enrolled (ie, Dose Level 3, Dose Level 4, etc) until the MTD has been exceeded, with individual dose increases not to exceed ≤ 50%. If Dose Level 1 is deemed to have exceeded the MTD, Dose Level -1 of INCB052793 (defined as 50%-75% of Dose Level 1) may be evaluated.

Part 2 Dose Expansion: This portion will explore the safety, tolerability, PK, [redacted] and preliminary clinical activity of the regimen identified in the dose-escalation portion through an optional expansion cohort of approximately 12 subjects per cohort, to be treated at the combination doses selected in Part 1.

Phase 2:

Phase 2 will include 2 treatment cohorts in which subjects with AML and high-risk MDS who failed prior therapy with HMA will receive INCB052793 in combination with azacitidine (Cohort I) or itacitinib in combination with azacitidine (Cohort J). A Simon 2-stage design will be used to evaluate the efficacy of the combination regimens in these cohorts. The approximate numbers of subjects for Stage 1 and Stage 2 are described in the Statistics section of the Protocol. If an insufficient number of responders are observed in the cohort at Stage 1, further enrollment in the cohort will be terminated.

Study Drugs, Dosage, and Mode of Administration

Phase 1a Monotherapy:

INCB052793 tablets (5 mg or 25 mg strength) will be administered orally QD, but dose escalation can be switched to twice daily as determined by emerging PK [redacted] data. The starting dose of INCB052793 will be 25 mg QD for TGA, and the PAD determined from TGA will be the starting dose for TGB subjects. INCB052793 will be self-administered in the fasted state as a QD oral treatment beginning on Cycle 1 Day 1 and daily thereafter in continuous 21-day cycles. Subjects will refrain from food consumption at least 2 hours before and 1 hour after study drug administration except on days when PK sampling is conducted, when subjects will refrain from food consumption at least 8 hours before and 1 hour after study drug or as indicated in the PK section. The tolerated regimen(s) (including the MTD or PAD of INCB052793) defined during the dose escalation will be used in the expansion. One cycle will be defined as 21 continuous days of planned study treatment.

Phase 1b Combination Therapy:

The starting dose of INCB052793 (ie, Dose Level 1) in the Phase 1b combination therapy will be approximately 50% to 100% of the PAD identified in Phase 1a. INCB052793 will be self-administered in the fasted state as a QD oral treatment beginning on Day 1 of Cycle 1, Day 1 of subsequent cycles, and daily thereafter in continuous 21-day (Cohorts D and H) or 28-day (all other cohorts) cycles. Subjects will refrain from food consumption at least 2 hours before and 1 hour after study drug administration except on days when serial PK [redacted] sampling is conducted, then subjects will refrain

from food consumption at least 8 hours before and 1 hour after study drug or as indicated in the PK section. A dose of INCB052793 that was evaluated and determined to be safe and tolerable during Part 1 will be used in Part 2.

Cohort A:

- *nab*-Paclitaxel will be administered as an open-label commercial product at a starting dose of 125 mg/m^2 intravenously (IV) over 30 minutes on Days 1, 8, and 15 of each 28-day cycle.
- Gemcitabine will be administered as an open-label commercial product at a starting dose of 1000 mg/m^2 IV over 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

Cohort B:

- Dexamethasone will be administered as open-label commercial product at a starting dose of 40 mg administered orally weekly on Days 1, 8, 15, and 22 of each 28-day cycle. If disease progression occurs after 1 or more cycles of the dexamethasone/INCB052793 combination, or if a response has not been achieved after 4 or more cycles (ie, stable disease), carfilzomib, bortezomib, or lenalidomide (at the discretion of the investigator) may be added to the regimen at a dose level that has been determined as safe and tolerable in the relevant treatment cohort (C, D, or E). If an additional agent is added to the regimen, the subject will subsequently follow the schedule of assessments appropriate to that agent.

Cohort C:

- Carfilzomib will be administered IV as an open-label commercial product at a dose of 20 mg/m^2 IV on Days 1 and 2 followed by 27 mg/m^2 IV on Days 8, 9, 15, and 16 of Cycle 1 and for all doses of each 28-day cycle thereafter. If disease progression occurs after 1 or more cycles of the combination, or if a response has not been achieved after 4 cycles (ie, stable disease), dexamethasone 40 mg administered orally weekly may be added to the regimen. After 12 cycles of carfilzomib treatment, subjects will transition to maintenance dosing on Days 1, 2, 15, and 16 of each 28-day cycle.

Cohort D:

- Bortezomib will be administered as an open-label commercial product at a dose of 1.3 mg/m^2 IV or subcutaneously (SC) on Days 1, 4, 8, and 11 of each 21-day treatment cycle. If disease progression occurs after 1 or more cycles of the combination, or if a response has not been achieved after 4 cycles (ie, stable disease), dexamethasone 40 mg administered orally weekly may be added to the regimen. After 8 cycles, subjects will transition to a maintenance schedule comprising 1 dose every 2 weeks.

Cohort E:

- Lenalidomide will be administered as an open-label commercial product at a starting dose of 25 mg administered orally QD on Days 1 through 21 of each 28-day cycle. Lower dose levels of lenalidomide may be explored (eg, 10 mg, 15 mg, 20 mg) based on the safety/tolerability of the combination. If disease progression occurs after 1 or more cycles of the combination, or if a response has not been achieved after 4 cycles (ie, stable disease), dexamethasone 40 mg administered orally weekly may be added to the regimen.

Cohort F:

- Azacitidine will be administered as an open-label commercial product at a dose of 75 mg/m^2 SC for 5 days, followed by 2 days of no treatment, then 75 mg/m^2 for 2 days of each 28-day treatment cycle. Intravenous administration is permitted if SC administration is not tolerated.

Cohort G

- Pomalidomide will be administered as an open-label commercial product at a dose of 4 mg administered orally QD on Days 1 through 21 of each 28-day cycle. Lower dose levels of pomalidomide may be explored (eg, 3 mg, 2 mg, 1mg) based on the safety/tolerability of the combination. Dexamethasone will be coadministered at 40 mg orally weekly on Days 1, 8, 15, and 22 of a 28-day cycle.

Cohort H

- The starting dose of INCB050465 will be 20 mg QD. Additional dose levels may be tested (eg, 30 mg or 15 mg) in combination with the recommended dose of INCB052793.

Based on safety assessments, individual subjects may have dose interruptions and/or reductions of INCB052793 or the applicable combination agent(s) during the course of treatment.

Phase 2:

Cohort I

- The starting dose of INCB052793 will be 35 mg QD.
- Azacitidine will be administered as above (ie, Cohort F).

Cohort J

- The starting dose of itacitinib will be 300 mg QD.
- Azacitidine will be administered as above (ie, Cohort F).

Based on safety assessments, individual subjects may have dose interruptions and/or reductions of INCB052793, itacitinib, or the applicable combination agent(s) during the course of treatment.

In Cohort J, the first 3 to 6 subjects will be monitored for occurrence of DLTs before enrollment of more subjects. If this dose exceeds the MTD, further subjects will be enrolled at 200 mg QD of itacitinib and monitored as above.

Duration of Participation:

Subjects will be treated in continuous 21-day cycles (Phase 1a and Phase 1b/Cohorts D and H) or 28-day cycles (Phase 1b/Cohorts A, B, C, E, F, and G, and Phase 2/Cohorts I and J) until they meet withdrawal criteria. If the subject discontinues all study treatment, the treatment portion will end and the subject will enter the follow-up portion. Study participation is expected to average about 6 months.

Study Population:

For Phase 1a monotherapy, the study population will consist of subjects diagnosed with an advanced malignancy who have failed, or are refractory to, available treatments.

For Phase 1b combination therapy, the study population will consist of subjects with advanced or metastatic pancreatic adenocarcinoma (first or second line), triple-negative breast cancer (second line), or urothelial cancer (second line) provided the subject is a candidate for treatment with gemcitabine and *nab*-paclitaxel (Cohort A), relapsed or refractory MM (Cohorts B, C, D, E, and G), AML/MDS (Cohort F), or lymphoma (Cohort H).

For Phase 2, the study population will consist of subjects with AML and high-risk MDS who failed prior therapy with HMA.

Key Inclusion Criteria for Phase 1a:

- Age 18 years or older
- Histologically or cytologically confirmed solid tumor (TGA) or hematologic malignancy (TGB). For Part 2 expansion, measurable or evaluable disease is required.
- Life expectancy of 12 weeks or longer.
- Must have received ≥ 1 prior treatment regimen and currently demonstrating progressive disease.
- Must not be a candidate for potentially curative or standard-of-care approved therapy.

Key Inclusion Criteria for Phase 1b:

- Age 18 years or older
- **Cohort A:** Histologically or cytologically confirmed pancreatic adenocarcinoma, triple-negative breast cancer, or urothelial cancer with at least 1 measurable or evaluable target lesion.

Cohorts B, C, D, E, and G: Histologically confirmed MM and measureable/evaluable disease as defined by 1 or more of the following:

- Serum M-protein ≥ 0.5 g/dL.
- Urine M-protein ≥ 200 mg/24 hours.
- Serum free light chain (FLC): involved FLC level ≥ 10 mg/dL provided serum FLC ratio is abnormal.

Cohort F: Confirmed AML or MDS (International Prognostic Scoring System intermediate-1 or -2, or high-risk) or MDS/myeloproliferative neoplasm (MPN) overlap syndromes in accordance with WHO diagnostic criteria, including chronic myelomonocytic leukemia (CMML), atypical BCR-ABL1–negative chronic myeloid leukemia, MDS/myeloproliferative neoplasm unclassifiable, and named refractory anemia with ring sideroblasts and thrombocytosis.

Cohort H: Individuals diagnosed with lymphomas who have failed or are refractory to available treatments.

- Subjects must not currently be a candidate for potentially curative hematopoietic stem-cell transplant and/or high-intensity chemotherapy.

- Prior therapy:

Cohort A: No more than 1 prior chemotherapy regimen for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy).

- There is no restriction on the number of prior nonmyelosuppressive targeted therapies; targeted therapy alone will not be considered chemotherapy for the purposes of this study.

Cohorts B, C, D, E, and G: Must have relapsed from or have been refractory to ≥ 2 prior treatment regimens, including a proteasome inhibitor and an immunomodulatory drug.

Cohort F: May have received any number of prior treatment regimens or be treatment-naive.

Cohort H: Must have relapsed from or have been refractory to available treatments.

- Subjects who have previously been discontinued from the standard-of-care agent (Cohorts A-G) or PI3Kδ inhibitors (Cohort H) being used in a specific cohort due to toxicity or intolerance may not enroll in that cohort (eg, subjects previously intolerant to bortezomib may not enroll in Cohort D).

Key Inclusion Criteria for Phase 2 (Cohorts I and J):

- Age 18 years or older
- Confirmed AML or high-risk MDS (International Prognostic Scoring System -2, or high risk) in accordance with WHO diagnostic criteria
- Failure of prior therapy with HMA, defined as one of the following:
  - progression to AML
  - 50% increase in bone marrow blasts
  - relapsed disease after response
  - at least 4 cycles of treatment without clinical benefit (hematological improvement [HI] or better).

Key Exclusion Criteria for Phase 1a, Phase 1b, and Phase 2:

- Prior receipt of a selective JAK1 inhibitor (Phase 1a only; prior receipt of ruxolitinib is permitted).
- Received an investigational study drug within 28 days or 5 half-lives (whichever is longer) before receiving the first dose of study drug, except if approved by the sponsor's medical monitor.
- Any approved anticancer medications within 21 days or 5 half-lives (whichever is longer) before receiving the first dose of study drug (42 days for nitrosoureas) or with medical monitor approval EXCEPT steroids at ≤ 10 mg prednisone daily (or equivalent; steroid exception does not apply to Phase 1b/Cohort B or G) and hydroxyurea to control blood counts.

- Any unresolved toxicity ≥ Grade 2 (except stable Grade 2 peripheral neuropathy and alopecia) from previous anticancer therapy.
  - Phase 1b/Cohort D may not have > Grade 1 peripheral neuropathy at baseline.
- Known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks before the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and have not required steroids for at least 7 days before study treatment.
- Eastern Cooperative Oncology Group (ECOG) performance status > 2.
- Any of the following laboratory results at screening without transfusions and hematopoietic growth factor support (except Phase 1b/Cohort F and Phase 2/Cohorts I and J):

Laboratory Parameter	Phase 1a/TGA and Phase 1b/Cohort A	Phase 1a/TGB and Phase 1b/Cohorts B through H Except F
Hemoglobin (g/dL)	< 10.0	< 8.0
Platelet count (10^9/L)	< 100	< 75
Absolute neutrophil count (10^9/L)	< 1.5	< 1.0

  - No specific hematologic exclusion criteria apply to Phase 1b/Cohort F and Phase 2/Cohorts I and J.
- Any of the following laboratory results at screening irrespective of causality, except if approved by the sponsor:
  - Conjugated bilirubin > 1.2 × upper limit of normal (ULN; need only be tested if total bilirubin exceeds > 1.5 × ULN). In Phase 2, Cohorts I and J, Stage 2: total bilirubin > 3 × ULN.
  - Alkaline phosphatase > 2.5 × ULN (or > 5 × ULN if bone metastases are present and hepatic parenchymal metastases are absent).
  - Aspartate aminotransferase or alanine aminotransferase > 3.0 × ULN (> 2.0 × ULN for Phase 1a/Part 1 and Phase 1b/Part 1). In Phase 2, Cohorts I and J, Stage 2: subjects with any AST value.
  - Creatinine clearance of < 60 mL/min (30 mL/min for subjects with MM and subjects in Phase 2, Cohorts I and J, Stage 2) measured or calculated by Cockroft-Gault equation or estimated glomerular filtration rate < 60 mL/min/1.73 m^2 (30 mL/min/1.73 m^2 for subjects with MM and subjects in Phase 2, Cohorts I and J, Stage 2) using the Modification of Diet in Renal Disease (MDRD) formula.
- Known human immunodeficiency virus infection.
- Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or risk of reactivation. Subject cannot be positive for HBV DNA, HCV RNA, hepatitis B surface antigen, or anti–hepatitis B core antibody, except if approved by the medical monitor.
- Any known contraindications to the use of gemcitabine, *nab*-paclitaxel, dexamethasone, carfilzomib, bortezomib, lenalidomide, pomalidomide, azacitidine, or PI3Kδ inhibitors (Phase 1b and Phase 2 only, as appropriate to treatment cohort).
- Ongoing radiation therapy and/or radiation therapy administered within 15 days of enrollment; subject must not require corticosteroids and must have recovered from all ongoing radiotherapy-related toxicities.
  - Subjects who have received radiation to the spine, pelvis, ribs, or femur should be discussed with the sponsor, as extensive radiation to a marrow-forming region may compromise a subject's ability to tolerate myelosuppressive chemotherapy.
- Current clinically active and uncontrolled infection of any etiology.

Study Schedule/Procedures:

Subjects will have scheduled study visits as follows:

Phase 1a Monotherapy:

- Screening
- Cycle 1 (21 days): Days 1, 8, and 15
- Subsequent cycles (21 Days): Day 1
- End of treatment
- Follow-up

Phase 1b and Phase 2 Combination Therapy:

- Screening
- Treatment cycles will be 21 or 28 days in length and will conform to the administration schedule of the relevant standard-of-care agent. Subjects in Cohorts C or D may switch to a maintenance schedule after a defined number of cycles.
- End of treatment
- Follow-up

Local laboratory tests: Study visits will include sample collection for hematology, chemistry, urinalysis, serology, and coagulation tests to be conducted at a local laboratory.

Central laboratory tests: The screening visit will include fertility/pregnancy testing conducted at a central laboratory. Additionally, study visits will include sample collection for expanded serum chemistry and serum pregnancy tests to be performed at a central laboratory. [redacted] PK samples will be collected at selected visits and shipped to Incyte or a central laboratory for analysis.

Clinical assessments: Electrocardiograms (ECGs), serial ECGs in Phase 1a/1b and Phase 2, physical examinations, ECOG performance status, disease assessments, and review of adverse events (AEs) will be performed by the investigative site.

Disease status assessments: An objective assessment of disease status will be performed at screening, appropriate to the malignancy type. Subsequent disease assessments should be performed per schedules of assessments.

Primary Endpoints:

Phase 1a and 1b:

- Safety and tolerability of INCB052793 monotherapy and in combination with standard therapies in select malignancies as assessed by summary of clinical laboratory assessments, 12-lead ECGs, and AEs.

Phase 2:

- ORR, defined as the proportion of subjects who achieve complete response (CR), CR with incomplete hematologic recovery, partial response, or HI, using the appropriate disease-specific criteria.

Secondary Endpoints:

- Response rates in those subjects with measurable disease as determined by investigator assessment of response.
- Safety and tolerability of INCB052793 in combination within azacitidine and of itacitinib in combination with azacitidine in subjects with AML and high-risk MDS who have failed prior therapy with HMA, assessed by summary of clinical laboratory assessments, 12-lead ECGs, and AEs.
- Pharmacokinetics of INCB052793 and itacitinib (Phase 1a, Phase 1b, and Phase 2) will be summarized.

- For Phase 1a Part 2 expansion portion (TGA and TGB), C_{max}, T_{max}, and AUC_{0-t} for Cycle 1 Day 1 and C_{max}, T_{max}, C_{min}, AUC_{0-t}, and $AUC_{0-\tau}$ for Cycle 1 Day 15, or C_{max}, T_{max}, C_{min}, AUC_{0-t}, and $AUC_{0-\tau}$ for Cycle 2 Day 1 in the case of food-effect evaluation.

[redacted]

Planned Number of Subjects: Up to approximately 141 subjects (36 subjects in Phase 1a, up to approximately 39 subjects in Phase 1b, and approximately 18-66 subjects in Phase 2).

Planned Number of Study Sites: Approximately 15 sites.

Estimated Study Duration: 58 months

- Estimated date first subject screened: July 2014
- Estimated date first subject dosed: August 2014
- Estimated date last subject completed: June 2019

Statistical Methods: Up to approximately 75 subjects will be enrolled in Phase 1a and Phase 1b. Approximately 18 to 66 subjects will be enrolled in Phase 2 based on the Simon 2-stage design. Descriptive statistics (eg, mean, standard deviation, range) will be derived where appropriate. Subject enrollment, disposition, demographics, and medical history will be summarized at baseline. The rate of DLTs will be summarized for each cohort. The overall response rate will be summarized as well. Safety and disease response data will be compared over time to assess change from baseline, during treatment, and follow-up. Pharmacokinetic [redacted] data will be analyzed with appropriate standard analytic software.

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LIST OF ABBREVIATIONS

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

Term	Explanation
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma or serum concentration-time curve
BID	twice daily
BCRP	Breast Cancer Resistant Protein
CI	confidence interval
CFR	Code of Federal Regulations
C_{max}	maximum observed plasma or serum concentration
CMML	chronic myelomonocytic leukemia
CR	complete response
CRi	complete response with incomplete hematologic recovery
CRF	case report form
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
dCTP	deoxycytidine triphosphate
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
[redacted]	[redacted]
EOT	end of treatment
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDG-PET	positron emission tomography using [^{18}F] fluorodeoxyglucose
FISH	fluorescence *in situ* hybridization
FLC	free light chain

Term	Explanation
GCP	Good Clinical Practice
GCSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practices
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HBC	hepatitis C virus
hERG	human ether-a-go-go related gene
HI	hematologic improvement
HIPAA	Health Insurance Portability and Accountability Act of 1996
HL	Hodgkin lymphoma
HMA	hypomethylating agent
HNSTD	highest non-severely toxic dose
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IL	interleukin
IMiD	immunomodulatory drug
IN	Investigator Notification
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
IMWG	International Myeloma Working Group
JAK	Janus kinase
MDRD	Modification of Diet in Renal Disease
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MM	multiple myeloma
NCCN	National Comprehensive Cancer Network

Term	Explanation
NHL	non-Hodgkin lymphoma
NOAEL	no-observed-adverse-effects level
NSCLC	non–small cell lung cancer
ORR	objective response rate
PAD	pharmacologically active dose
PJP	*Pneumocystis jiroveci* pneumonia
PD	pharmacodynamics
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PI3K	phosphatidylinositol 3-kinase
PI3Kδ	phosphatidylinositol 3-kinase δ
PK	Pharmacokinetic
PO	orally
PT	prothrombin time
PTT	partial thromboplastin time
PR	partial response
QTcF	QT interval corrected using the Fridericia formula
QD	once daily
RA	rheumatoid arthritis
SAE	serious adverse event
SC	subcutaneously
STAT	signal transducers and activators of transcription
STD10	severely toxic dose in 10% of animals
SCM	stromal conditioned media
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TGA	Treatment Group A
TGB	Treatment Group B
T_{max}	time to maximum plasma concentration
TYK	tyrosine kinase
ULN	upper limit of normal
Vd_{ss}	volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

INCB052793 hydrochloride, referred to herein as INCB052793, is an inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases (TYK), with selectivity for JAK1. INCB052793 is an investigational product that is in development for treatment of patients with advanced or metastatic cancer. Janus kinases play an important role in signal transduction after cytokine and growth factor binding to their receptors. Aberrant production of cytokines and growth factors has been associated with a number of cancers. Additionally, the JAK/signal transducers and activators of transcription (STAT) pathway is a progrowth signaling pathway, direct or indirect activation of which has been observed in a variety of tumor types. Therefore, JAK inhibitors represent potential therapeutic agents for these disease states.

1.1.1. Janus Kinases in Oncology

The JAK enzymes play an obligatory role in transducing intracellular signals generated by cytokine and growth factor receptors. Upon cytokine and growth factor binding to their cognate receptors, tyrosine phosphorylation of the intracellular domains of the receptors by JAKs enables them to serve as docking sites for STAT transcription factors, which are also phosphorylated. Tyrosine phosphorylated STATs are released from the receptors, form homodimers, and translocate to the nucleus where they bind canonical sequences and modulate transcription of genes that regulate a number of cellular functions (Sansone and Bromberg 2012). In contrast to normal cells, in which STAT tyrosine phosphorylation occurs transiently, STAT proteins, especially STAT3, are persistently phosphorylated in most malignancies (Sansone and Bromberg 2012). The persistent or constitutive phosphorylation of STAT3 in cancers may occur via a variety of mechanisms, including a) increased expression of cytokines and cytokine receptors, b) decreased expression of the negative regulatory proteins such as suppressors of cytokine signaling through promoter methylation, and c) loss of tyrosine phosphatases that dephosphorylate JAKs and STATs.

Neoplastic progression involves JAK/STAT pathway activity through cell autonomous and non-cell autonomous mechanisms. Cell autonomous mechanisms refer to tumor cell intrinsic alterations that facilitate the gain of neoplastic properties. The ability of STAT3 to sustain cell proliferation and block apoptosis (Lesina et al 2011); mediate cell cycle progression during oncogenic stress (Toyonaga et al 2003, Thoennissen et al 2009); control invasiveness, metastasis, and angiogenesis; and confer chemotherapeutic resistance (Catlett-Falcone et al 1999) are major mechanisms contributing to cancer. Non-cell autonomous mechanisms refer to the extrinsic effects mediated by tumor microenvironment, stroma, immune system, and stellate cells (Masamune et al 2005); these play an integral role in many cancers and are substantially shaped to a great extent by JAK/STAT signaling. In addition, JAK/STAT-dependent inflammatory cytokines such as interleukin (IL)-6 and interferon gamma are critical mediators of cancer cachexia, a significant cause for cancer morbidity and mortality. Based on this evidence, we hypothesize that inhibition of JAK kinases may directly affect malignant cell proliferation and may suppress the inflammatory state leading to improvements in nutritional status, fatigue, tolerance to therapy, and prolonged survival in patients with advanced cancers that are driven by

these intrinsic and extrinsic pathways influenced by STATs. This hypothesis is supported by evidence that JAK/STAT inhibitors are able to slow tumor cell growth and prolong survival in *in vivo* models (Thoennissen et al 2009, Toyonaga et al 2003, Iwanski et al 2010, Burger et al 2009, Li et al 2010).

1.1.2. Pharmacology of INCB052793

INCB052793 is a small molecule inhibitor of the JAK family of protein TYKs, with selectivity for JAK1, which is proposed for development for the treatment patients with advanced or metastatic cancer. Janus kinases play an important role in signal transduction following cytokine and growth factor binding to their receptors. Aberrant production of cytokines and growth factors has been associated with a number of cancers. Additionally, the JAK/STAT pathway is a progrowth signaling pathway; direct or indirect activation of which has been observed in a variety of tumor types. Therefore, JAK1 inhibition may be efficacious in these diseases.

In vitro, INCB052793 potently inhibits JAK1 (IC_{50} = 1.8 nM), with 18 to > 800-fold selectivity over the other JAK family members, JAK2, JAK3, and TYK2. INCB052793 also demonstrates JAK1 selectivity in cell-based assays. In cell-based assays previously shown to be dependent on JAK1 activity, including IL-2 or IL-6 stimulated phosphorylation of STATs; INCB052793 showed potent inhibition with IC_{50} values in the range of approximately 10-100 nM. In human whole blood, INCB052793 inhibited IL-6–stimulated phosphorylated STAT3 (pSTAT3) with an IC_{50} value of 144 nM, and showed approximately 100-fold weaker activity in blocking pSTAT3 induced by thrombopoietin, a cytokine that is known to signal through JAK2 homodimers (IC_{50} = 14110 nM). In addition to its effects on JAK-mediated signaling, INCB052793 potently inhibited the production of proinflammatory factors (eg, IL-17, monocyte chemoattractant protein 1 [MCP-1]) induced by other cytokines, such as IL-23 and IL-6, with IC_{50} values in the range of approximately 10 to 100 nM. Finally, INCB052793 was shown to block the cytokine-dependent growth of tumor cell lines *in vitro*, with IC_{50} values in the range of 100nM to 250 nM. These results confirm that INCB052793 shows consistent pharmacological activity in cell-based assays and displays selectivity for JAK1 versus JAK2 in both biochemical and cellular assays.

In vivo, INCB052793 potently and dose-dependently inhibited JAK/STAT signaling in a number of different tumor models, including pancreatic ductal adenocarcinomas. As a single agent, treatment with INCB052793, when administered either by continuous infusion or by oral gavage, was sufficient to inhibit the growth of cytokine-dependent INA-6 myeloma. Both the pharmacodynamic (PD) effects and tumor growth inhibitory activity were observed at plasma concentrations of INCB052793 below that required to inhibit JAK2 in a biologically relevant milieu in humans or rats. These data are consistent with the concept that selective JAK1 inhibition may be efficacious in a number of oncological diseases.

In safety pharmacology assessments of INCB052793, including a series of *in vitro* binding and enzyme assays, respiratory and central nervous system (CNS) studies in rats, and *in vitro* the human ether-a-go-go related gene (hERG) and *in vivo* (conscious telemeterized dogs) cardiovascular studies, no adverse findings were noted. Therefore, the risk associated with clinical administration of INCB052793, stemming from the pharmacology of this molecule, is expected to be low.

In summary, pharmacological data obtained in both *in vitro* and *in vivo* model systems support the potential utility of orally administered INCB052793 in the treatment of advanced or metastatic disease.

1.1.3. Absorption, Distribution, Metabolism, Excretion and Disposition

1.1.3.1. Absorption

The *in vitro* permeability of INCB052793 across Caco-2 monolayers was moderate (5.7×10^{-6} cm/s). INCB052793 is a substrate of both P-glycoprotein (P-gp) and Breast Cancer Resistant Protein (BCRP). Since INCB052793 is a substrate of P-gp at concentrations below 100 μM *in vitro*, it is unlikely that efflux by P-gp plays an important role in the oral absorption of INCB052793. However, efflux by BCRP was not saturated at 100 μM *in vitro*. Thus, BCRP may limit oral absorption at the lower proposed clinical dose. In single dose, oral pharmacokinetic (PK) studies conducted in rats, dogs, and monkeys, INCB052793 was absorbed slowly in monkeys, with T_{max} values of 3.5 hours, while this value was 0.75 hours and 0.94 hours in dogs and rats, respectively. The absolute oral bioavailability was low in monkeys (19%) but high in dogs (84%) and was complete in rats.

1.1.3.2. Distribution

In single-dose, intravenous (IV) administration PK studies in rats, dogs, and monkeys, the apparent steady-state Vd_{ss} values of INCB052793 ranged from 0.902 to 1.77 L/kg, suggesting that INCB052793 is distributed slightly beyond the total volume of body water (0.7 L/kg) in these 3 preclinical species.

INCB052793 exhibits low protein binding in rats, dogs, and human with the fraction unbound being approximately 50% and independent of substrate concentration. In rats and beagle dogs, the fraction unbound was similar between *in vitro*- and *ex vivo*-sourced plasma. The average e*x vivo* fraction unbound of INCB052793 in both rat and dog plasma was 55%, and the average *in vitro* fraction unbound of INCB052793 in human plasma and serum was 51 %. The total brain concentration of INCB052793 after 4 hours of infusion was 11% of the corresponding total plasma concentration in the same rats, and the cerebrospinal fluid (CSF) concentration was 9.4% of the corresponding estimated unbound plasma concentration. Therefore, based on observed concentrations in the brain and CSF, it is concluded that INCB052793 has limited penetration across the blood-brain-barrier in rats.

Although INCB052793 is an inhibitor of P-gp, with an IC_{50} of 65.5 μM, potential for a clinical drug-drug interaction with a P-gp substrate is low at clinically relevant exposures. However, INCB052793 is a substrate of both P-gp and BCRP, and hence a clinical drug interaction study with inhibitors of P-gp and BCRP may be warranted.

1.1.3.3. Metabolism

In PK studies, INCB052793 exhibited low systemic clearance in rats and beagle dogs but moderate systemic clearance in cynomolgus monkeys, corresponding to 20%, 21%, and 42% of hepatic blood flow in these species, respectively.

In vitro metabolism studies showed that cytochrome P450 (CYP) 2D6, CYP3A4, UGT1A9, and UGT2B7 metabolize INCB052793. INCB052793 was not a potent inhibitor of human liver

microsomal CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4-mediated testosterone hydroxylation activity, with IC_{50} values > 25 μM, but was an inhibitor of CYP3A4-mediated midazolam hydroxylation activity, with an IC_{50} value of 13 μM. There was no evidence of metabolism-dependent inhibition of CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Thus, INCB052793 is unlikely to cause clinical drug interactions via inhibition of CYPs at the proposed therapeutic dose (50 mg once daily [QD]). Following repeated dose administration in rats and dogs, there was no evidence of auto-induction of clearance.

The *in vitro* metabolism of INCB052793 in preclinical species was generally low to moderate, with the greatest amount of turnover noted in the monkey. In the hepatic microsomal samples, S-9 fractions and hepatocyte incubations across all species, a total of 11 metabolites were detected by liquid chromatography-mass spectrometry (LC-MS). The most abundant metabolites were oxidative metabolites M8 in monkey S-9 and hepatocytes, M4 in rat microsomes, and the glucuronide conjugate of INCB052793 (M13) in monkey hepatocytes. Overall, there were only minor quantitative and qualitative differences evident between the species. There were no human-specific metabolites noted in the course of this investigation. Trace amounts of 2 glutathione conjugates were likely formed by *in vitro* rat metabolites M1 and M2, but these conjugates were not found in human liver microsomes.

There were no major metabolites observed in rat plasma, but several metabolites were observed at trace levels. In dog plasma, 2 major metabolites of INCB052793, M4 and M11, were identified with several metabolites being observed at trace levels. A total of 7 metabolites of INCB052793 were found and characterized in urine samples from rats and dogs. The most abundant metabolites were M4, M7, and M11 in rat urine, and M11 in dog urine.

1.1.3.4. Excretion

Based on PK studies with unlabeled INCB052793, the renal excretion of intact INCB052793 was low (less than or approximating the GFR in preclinical species), suggesting that active renal tubular secretion is not likely involved in the renal excretion of INCB052793 in these 3 species.

1.1.3.5. Disposition

Following IV administration of INCB052793, the total systemic clearance was low in rats (0.667 L/h/kg) and beagle dogs (0.396 L/h/kg) and moderate in monkeys (1.10 L/h/kg), which approximated 20%, 21%, and 42% of hepatic blood flow in these species, respectively. After IV administration, INCB052793 had a moderate half-life in rats (3.5 hours) and dogs (3.1 hours), while this value was long in monkeys (6.8 hours).

1.2. Standard-of-Care Agents

1.2.1. Gemcitabine

Gemcitabine is a nucleoside analog with structural similarity to cytarabine and is currently approved to treat breast cancer, non–small cell lung cancer (NSCLC), ovarian cancer, and pancreatic cancer either alone or in combination with other chemotherapy agents. Gemcitabine has also shown efficacy in other tumor types and is currently being studied in various advanced and metastatic cancers.

Gemcitabine monotherapy was approved by the FDA in 1996 as first-line treatment for patients with locally advanced or metastatic adenocarcinoma of the pancreas that was previously treated with fluorouracil. Clinical benefit and survival were used as the primary endpoints in a study that included 126 previously untreated patients randomly assigned to fluorouracil or gemcitabine (Argilés et al 2009, Burris et al 1997). Although there were no confirmed objective responses in either group, gemcitabine was associated with significantly better clinical response (24% vs 5%) and 1-year survival (18% vs 2%). Although monotherapy gemcitabine demonstrated improvement of overall survival in advanced or metastatic pancreatic cancer, gemcitabine is more commonly administered as part of a combination regimen in other tumor types.

Gemcitabine is also approved for use in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced, or metastatic NSCLC, and in combination with paclitaxel for the treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant therapy. The most recent approval is for the use of gemcitabine in combination with carboplatin in patients with advanced ovarian cancer. All studies conducted showed a significant improvement in time to disease progression, progression-free survival (PFS), and objective tumor response in the gemcitabine treatment arm versus the comparator. Improvement in overall survival with gemcitabine has been demonstrated in NSCLC and metastatic breast cancer; however, no significant difference in overall survival was observed in combination with carboplatin in ovarian cancer.

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate and triphosphate nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis; this inhibition causes a reduction in the concentrations of deoxynucleotides, including deoxycytidine triphosphate (dCTP). Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. A drug-drug interaction between INCB052793 and gemcitabine is not anticipated based on the mechanism of clearance of both compounds.

1.2.2. Gemcitabine Plus *nab*-Paclitaxel

Activity for gemcitabine in combination with *nab*-paclitaxel in pancreatic cancer has been shown in a Phase 2 study (Von Hoff et al 2011) and in a recently completed Phase 3 study (Von Hoff et al 2013). In the Phase 3 study, among subjects treated with gemcitabine 1000 mg/m^2 with or without *nab*-paclitaxel 125 mg/m^2 on Days 1, 8, and 15 of every 28-day cycle, *nab*-paclitaxel demonstrated a 31% reduction in the risk of progression or death, with a median PFS of 5.5 versus 3.7 months and an overall response rate of 23% compared to 7% with gemcitabine alone. The most common Grade 3 or greater treatment-related adverse events (AEs) were neutropenia (38% vs 27%), fatigue (17% vs 7%), and neuropathy (17% vs 1%) in the combination arm versus the gemcitabine-only arm. There was no difference in serious life-threatening toxicity (4% in each arm).

Gemcitabine in combination with paclitaxel has demonstrated activity in metastatic breast cancer, with improvements in PFS and overall survival (Park et al 2013). The combination of gemcitabine and paclitaxel has also been used effectively in second-line urothelial cancer (Ikeda et al 2011, Albers et al 2011). Thus, gemcitabine in combination with paclitaxel has

shown clinically meaningful antitumor activity in first- and/or second-line metastatic pancreatic, breast, and urothelial cancer. Treatment with *nab*-paclitaxel delivers paclitaxel to the tumor as the active moiety, and treatment with *nab*-paclitaxel has been shown to permit greater dose intensity with reduced toxicity compared with paclitaxel (Abraxane 2013). Thus, the combination of gemcitabine with *nab*-paclitaxel is currently being used in indications where the combination of gemcitabine with paclitaxel has shown activity.

nab-Paclitaxel promotes the assembly and stability of microtubules, resulting in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. The PK of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are inducers or inhibitors of CYP2C8 and/or CYP3A4. INCB052793 is primarily metabolized by CYP3A4 but is not an inducer or inhibitor of CYP3A4 at clinically relevant concentrations. A metabolic drug-drug interaction between INCB052793 and *nab*-paclitaxel is not anticipated.

1.2.3. Dexamethasone

Dexamethasone is a synthetic adrenocortical steroid that is FDA-approved for use in several endocrine, inflammatory, and autoimmune conditions (Dexamethasone 2007), as well as palliative treatment for hematologic malignancies, including leukemia and lymphoma. Dexamethasone and other glucocorticoids exert apoptotic effects on myeloma cells, in part through inhibition of NF-κB activity (Greenstein et al 2002). Pulse dexamethasone has been used as a single agent in the treatment of primary and relapsed/refractory multiple myeloma (MM) since the early 1980s (Facon et al 2006). Overall single agent response rates of 43% (Alexanian et al 1992) and 21% (Alexanian et al 1986) have been reported in the primary and treatment refractory settings, respectively. Dexamethasone is a weak inducer of CYP3A4, but it is not expected to exert pharmacologically significant or clinically relevant decreases in INCB052793 concentration.

1.2.4. Carfilzomib

Carfilzomib is a second-generation proteasome inhibitor that has been approved in the United States since 2012 for treatment of patients with relapsed and/or refractory MM (Kyprolis 2012). Carfilzomib is structurally and mechanistically different from the dipeptide boronic acid proteasome inhibitor bortezomib, which has been approved since 2003 for use in the treatment of patients with MM. Carfilzomib has demonstrated activity in relapsed or refractory MM both as a single agent (Siegel et al 2012) and in combination with other antimyeloma agents, including dexamethasone (Badros et al 2013) and immunomodulatory agents such as lenalidomide (Niesvizky et al 2013, Richardson et al 2014b, Papadopoulos et al 2015). Carfilzomib is a tetrapeptide with an epoxyketone and is metabolized by peptidases; a metabolic drug-drug interaction between INCB052793 and carfilzomib is not anticipated.

1.2.5. Bortezomib

Bortezomib is a proteasome inhibitor that has been approved in the United States since 2003 for treatment of patients with MM (Velcade 2014). Bortezomib exerts a number of different antimyeloma effects, including disruption of the cell cycle and induction of apoptosis, alteration of the bone marrow microenvironment and inhibition of NF-κB (Field-Smith et al 2006). The Phase 3 APEX trial evaluating single-agent bortezomib versus high-dose dexamethasone in

relapsed MM reported partial and complete response (CR) rates of 43% and 9%, respectively, in the bortezomib group (Richardson et al 2007). Single-agent bortezomib has also been demonstrated to prolong time to progression and overall survival relative to high-dose dexamethasone in patients with relapsed MM (Richardson et al 2007) The addition of dexamethasone has also been shown to augment responses after disease progression or lack of response on single-agent bortezomib (Jagannath et al 2006). Bortezomib is a substrate of CYP enzyme 3A4, 2C19, and 1A2, but is not an inhibitor or inducer. A metabolic drug-drug interaction between INCB052793 and bortezomib is not anticipated.

1.2.6. Lenalidomide

Lenalidomide is a thalidomide analogue that has been FDA-approved for treatment of MM since 2005 (Revlimid 2015). Several mechanisms are known to be responsible for the antimyeloma activity of lenalidomide; these include immunomodulatory, anti-angiogenic, and direct antineoplastic effects (Kotla et al 2009). Richardson et al (2006) demonstrated a single-agent overall response rate of 25% in relapsed/refractory MM; in subjects who did not achieve a response after 2 cycles, dexamethasone was added and the overall response rate in the combination group was 29%. Two Phase 3 studies (Dimopoulos et al 2007, Weber et al 2007) evaluated the combination of lenalidomide and dexamethasone versus dexamethasone alone; these studies revealed an overall response rate of 60.2% versus 24% and 61% versus 19.9%, respectively. Lenalidomide is a P-gp substrate but not an inhibitor, and it also is not a CYP inhibitor or inducer. A metabolic drug-drug interaction between INCB052793 and lenalidomide is not anticipated.

1.2.7. Azacitidine

Azacitidine is a nucleoside metabolic inhibitor that is approved by the FDA for the treatment of patients with several different subtypes of myelodysplastic syndrome (MDS; Vidaza 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 (Fenaux et al 2009) evaluating azacitidine versus conventional care in higher risk MDS revealed superior rates of hematological response (29% vs 12%) and hematological improvement (49% vs 29%) in the azacitidine group.

Azacitidine is recommended as a low-intensity induction therapy in acute myeloid leukemia (AML), primarily in patients who are unfit for high- or intermediate-intensity regimens (NCCN Guidelines). 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 INCB052793, itacitinib, and azacitidine is not anticipated.

1.2.8. Pomalidomide

Pomalidomide is approved for the treatment of MM (in combination with dexamethasone) in patients who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor, and have demonstrated disease progression on or within 60 days of completion of the last therapy. In the United States, approval was granted in 2013 on the basis of 2 Phase 2 clinical studies in which pomalidomide and dexamethasone showed objective response rate (ORR) of 29% and 34%, respectively. European Medicines Agency approval was granted later that year based on the results of the aforementioned Phase 2 clinical studies in addition to the results of a Phase 3 open-label study that compared the efficacy and safety of pomalidomide plus low-dose dexamethasone with high-dose dexamethasone, which benefits PFS (4.0 months vs 1.9 months), ORR (31% vs 10%), and overall survival (12.7 months vs 8.1 months). The doses of pomalidomide (4 mg orally [PO] on Days 1 to 21 of each 28-day cycle) and dexamethasone (40 mg orally weekly on Days 1, 8, 15, and 22 of a 28-day cycle) used in each of the above studies are the recommended doses in the relevant approvals, with appropriate adjustments for toxicities.

1.3. Overview of INCB050465

INCB050465 represents a novel, potent, and selective inhibitor of the Class IA phosphatidylinositol 3-kinase (PI3K) enzymes, with selectivity for the delta isoform, which is proposed for development for treatment of hematological malignancies. Because aberrant activation of phosphatidylinositol 3-kinase δ (PI3Kδ) has been associated with increased malignant B-cell proliferation and survival, its inhibition may be therapeutic for the treatment of such conditions.

1.3.1. Pharmacology of INCB050465

INCB050465 potently inhibits the PI3Kδ kinase (IC_{50} = 1.0 ± 0.5 nM), with approximately 20,000-fold selectivity for the other PI3K family members and > 300-fold selectivity against a broad panel of 192 other kinases. INCB050465 also showed no significant cross-reactivity (defined as > 50% inhibition of specific binding) when screened *in vitro* at 0.1 and 1.0 μM against approximately 70 receptors, ion channels, transporters, and enzymes. Moreover, INCB050465 is potent (IC_{50} values of ≤ 10 nM) in cell-based assays relevant to the pathogenesis of B-cell malignancies, such as PI3Kδ-mediated signaling and growth of human B-cell lines. This effect is not due to general cytotoxicity, because 10 μM INCB050465 had no significant effect on the growth of nonlymphoid cell lines. Compared to inhibition of B-cell proliferation, INCB050465 is similarly potent in blocking helper T-cell differentiation but is > 100 times less potent in assays that measure effects on human T-cell and natural killer cell proliferation or monocyte function. [redacted] *In vivo*, INCB050465 administration inhibited PI3Kδ signaling and tumor growth as a single agent in a dose-dependent manner in Pfeiffer xenograft models of non-Hodgkin lymphoma (NHL).

These data are further discussed in the INCB050465 Investigator's Brochure (IB).

1.3.2. Nonclinical Drug Metabolism and Pharmacokinetics of INCB050465

The absorption, distribution, metabolism, and excretion of INCB050465 have been studied in rats, dogs, and monkeys. INCB050465 exhibited low systemic clearance, a low to moderate volume of distribution, moderate (4 to ~9 hours) terminal half-life, and good absorption, with the absolute oral bioavailability ranging from 74% to 100%.

After IV administration, INCB050465 displayed low systemic clearance, representing 26%, 2%, and 5% of the hepatic blood flow in rats, dogs, and monkeys, respectively. The steady-state volume of distribution was moderate in rats (1.5 L/kg) but low in dogs (0.3 L/kg) and monkeys (0.8 L/kg), implying species differences. The terminal elimination half-life ranged from 4.0 hours (rat) to 9.3 hours (monkey). The renal excretion of intact INCB050465 was minimal (< 2% across species). INCB050465 has limited penetration across the rat blood-brain barrier.

The *in vitro* permeability of INCB050465 across Caco-2 monolayers was low (0.99×10^{-6} cm/s). As INCB050465 is a substrate for P-gp at concentrations below 100 μM, oral absorption is not expected to be compromised by efflux at higher doses. In single oral dose PK studies conducted in rats, dogs, and monkeys, INCB050465 was absorbed rapidly, with T_{max} values ranging from 0.3 to 2.5 hours. After oral administration, the bioavailability of INCB050465 was complete in dogs (100%) and high in monkeys (80%) and rats (74%).

The protein binding of INCB050465 was determined in serum and plasma obtained from rats, beagle dogs, and human (*in vitro* and *ex vivo*). The *in vitro* fraction unbound of INCB050465 was similar in plasma from dog and human (4.6% and 7.6%, respectively), with the fraction unbound somewhat higher in plasma from rat (23%). For rats and beagle dogs, the average *ex vivo* fractions unbound of 16.5% and 3.5%, respectively, are used for safety margin calculations, while for humans, the average data from plasma and serum of 7.4% are used.

INCB050465 is metabolized primarily by CYP3A4. INCB050465 is not an inhibitor of the major CYPs evaluated, nor is it an inducer of CYP3A4. In addition, there were no human-specific metabolites noted using *in vitro* systems. There is no evidence of chemical reactivity subsequent to metabolism.

These data are further discussed in the INCB050465 IB.

1.3.3. Potential Risks of INCB050465 Based on Preclinical Safety

Based on findings in repeat-dose toxicity studies of INCB050465 in rats and dogs, lymphoid depletion and resulting immunosuppression represents a potential risk for humans.

Repeat-dose toxicity of INCB050465 was evaluated after QD administration for 28 days in Sprague Dawley rats at doses of 10 mg/kg, 30 mg/kg, and 100 mg/kg per day, and beagle dogs at doses of 1 mg/kg, 3 mg/kg, and 15 mg/kg per day. Recovery was evaluated after a 4-week nondosing period in both species.

In both rats and dogs, immunosuppression (evident as minimal to marked depletion of lymphoid tissues, including thymus, lymph nodes, spleen, and gut-associate lymphoid tissue) was observed at all doses and considered to be consistent with the pharmacologic activity of INCB050465. The incidence and severity of these findings increased with dose.

Moderate bone marrow depletion and/or fibrosis occurred in 2 female rats at 100 mg/kg per day (exposure at this dose in female rats is approximately 190-fold higher than projected human

exposure [unbound AUC] after 10 mg), no changes in bone marrow were observed in the rat at lower doses or at the end of the recovery period; also, there were no changes in bone marrow on the dog studies. Septicemia/bacterial pancreatitis, considered secondary to immunosuppression, led to the death of 1 female rat at 100 mg/kg per day.

Dose-related minimal to mild hypospermatogenesis was observed in male rats at 30 and 100 mg/kg per day, which demonstrated recovery after 28 days.

In dogs, effects secondary to immunosuppression included subacute inflammation in multiple tissues, including lymphoid tissue, gastrointestinal tract, liver, lungs, kidney, and bladder. Severe acute inflammation of the lung and gastrointestinal tract led to early death or sacrifice of 1 female dog at 3 mg/kg per day and 1 male dog at 15 mg/kg per day, respectively.

There were no findings in dogs indicative of any off-target toxicity. Increases in alkaline phosphatase (ALP; 3.5- to 4-fold over control) and alanine aminotransferase (ALT; 1.7- to 4.7-fold over control) were observed at 15 mg/kg per day and correlated with minimal to moderate, acute to subacute inflammation and minimal to mild single-cell necrosis attributed to immunosuppression and systemic spread of microbes. Complete recovery for these changes was observed.

Based on the severity of findings at higher doses, including bone marrow depletion/fibrosis in rats and secondary effects leading to early death in both species, the highest nonseverely toxic dose was considered to be 30 mg/kg per day in rats and 1 mg/kg per day in dogs. These doses and associated exposures are well above the intended clinical starting dose in this study and the anticipated therapeutic dose in humans.

In exploratory studies in rats, evidence of hepatotoxicity was seen. These liver findings included periportal inflammatory cell infiltrates accompanied by minimal biliary hyperplasia and were observed at doses of ≥ 100 mg/kg per day. These findings were not reproduced in a 28-day GLP study in doses less than 100 mg/kg per day. Plasma exposures in rats administered ≥ 100 mg/kg per day were > 65-fold higher than the project clinical exposure at a dose of 10 mg QD.

INCB050465 was not mutagenic or genotoxic in a bacterial reverse mutation assay, *in vitro* chromosomal aberrations study in human peripheral blood lymphocytes, or rat *in vivo* micronucleus assay.

1.3.4. Clinical Summary of INCB050465

INCB050465 is currently being evaluated in a Phase 1/2 study in subjects with previously treated B-cell malignancies. As of 04 DEC 2015, 15 subjects have been treated in the dose escalation portion of Study INCB 50465-101. No dose-limiting toxicities (DLTs) were seen during dose escalation of 5 mg QD (n = 1), 10 mg QD (n = 3), 15 mg QD (n = 3), 20 mg QD (n = 4), or 30 mg QD (n = 4). Dose-limiting toxicity observation is ongoing for the 45 mg QD cohort. Four subjects discontinued treatment, 3 due to disease progression and 1 due to AE (Grade 2 exfoliative dermatitis). Seven Grade ≥ 3 treatment-emergent adverse events (TEAEs) were seen in 5 subjects: anemia, bacteremia, Escherichia infection, neutropenia, sepsis, syncope, and white blood cell count decreased; none were considered treatment-related. To date, only Grade 1 transaminase elevations have been observed. Target inhibition as assessed by pAKT levels in peripheral blood showed > 80% inhibition at trough in subjects receiving 5 mg, 10 mg, 15 mg, 20 mg, or 30 mg QD of INCB050465. Tumor responses have been observed in subjects with a

broad range of B-cell malignancies, receiving INCB050465 at a doses ranging from 10 to 30 mg QD. Among 12 efficacy-evaluable subjects, responses were observed in diffuse large B-cell lymphoma (DLBCL; 2/5 subjects), follicular lymphoma (2/2), chronic lymphocytic lymphoma (CLL; 1/2), mantle cell lymphoma (1/1), and marginal zone lymphoma (1/1). Clinical benefit was observed early in the course of treatment, and the longest duration of response was 17+ weeks. Pharmacodynamic assays have demonstrated that maximum measurable target inhibition is also achieved with doses of $\geq$ 10 mg QD. Therefore, the pharmacologically active dose (PAD) has been reached for this compound.

1.3.5. Clinical Pharmacokinetics of INCB050465

Preliminary PK results are available from 13 subjects in 5 cohorts treated with INCB050465 monotherapy in the ongoing Phase 1/2 study. Following fasting oral administration, INCB050465 was absorbed rapidly, typically attaining peak plasma concentrations within 0.5 to 1 hour after administration. INCB050465 plasma concentrations subsequently declined in a monophasic or biphasic fashion with mean terminal-phase disposition $t_{½}$ from 7.9 to 11.5 hours, similar to the 12 hours projected by preclinical data. INCB050465 exhibited low oral-dose clearance ranged with mean values from 1.49 to 4.07 L/hr. Though mean C_{max} and AUC increased less than proportional on Cycle 1 Day 15, approximate dose proportionality was observed over 5 mg to 30 mg on Cycle 1 Day 1. However, the caveats are (a) limited number of subjects, for example, N = 1 at 5 mg, (b) inter- as well as intra-individual variability within each dose group, and (c) relatively narrow dose range evaluated to date. The mean trough concentrations on Cycle 1 Day 15 for all 5 cohorts exceeded the projected IC_{90} for inhibition of PI3Kδ signaling in tumor cells, and the steady state was reached on or before Cycle 1 Day 8.

1.3.6. Overview of the Combination of INCB052793 and INCB050465

1.3.6.1. Rationale for Combining Inhibition of JAK1 and PI3Kδ

Janus kinase/STAT and PI3K pathways may contribute to driving tumor growth and survival in lymphomas, and combination therapies that block both pathways may prove more beneficial due to the central role that JAK-mediated cytokine signaling plays in augmenting BCR-mediated activation of the NF-κB pathway. To test this hypothesis preclinically, a panel of DLBCL cell lines was grown in conditions to activate the JAK pathway. These cells lines were exposed to the PI3Kδ inhibitor INCB040093, either alone or in combination with a panel of compounds that were shown to selectively inhibit JAK1 to examine their effects on cell proliferation and signaling. The JAK pathway was not constitutively activated when grown in the absence of stromal conditioned media (SCM), IL-6, or IL-10 as assessed by the levels of pSTAT3, a direct downstream target of JAK proteins. In addition, IL-6 or SCM, which contains predominantly IL-6, IL-8, and granulocyte-colony stimulating factor, failed to activate the pathway in the majority of cell lines. In contrast, IL-10 activated the JAK/STAT pathway in the majority of cell lines tested, consistent with previous reports (Gupta et al 2012).

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

JAK/STAT3 activation is characteristic of multiple T-cell lymphomas, including anaplastic large cell lymphoma (ALCL), peripheral T-cell lymphomas, and others. In anaplastic lymphoma kinase–negative ALCL, 38% of cases were found to carry mutations leading to constitutive activation of the JAK/STAT3 pathway, including mutations of JAK1, STAT3, translocation (NFκB2-ROS1 and NFκB2-TYK2). Similar findings were found in peripheral T-cell lymphomas and Sézary syndrome, which were found to harbor activating JAK or STAT mutations in 36% and 11%, respectively, of cases studied. *In vitro* and *in vivo* studies

demonstrate sensitivity of these tumors to JAK1/JAK2 inhibition (Kiel et al 2015, Kiel et al 2014).

Clinically, the combination of PI3Kδ inhibition and JAK1 inhibition has been tested in Study INCB 40093-102. Preliminary activity has been observed in subjects with NHL and Hodgkin lymphoma (HL) receiving INCB040093 monotherapy and combination treatment (data on file).

1.3.6.2. Nonclinical Pharmacokinetics and Drug Metabolism of the Combination of INCB052793 and INCB050465

Both INCB050465 and INCB052793 are metabolized predominately by CYP3A4 but neither appears to be an inducer or inhibitor of CYP3A4 at clinically relevant concentrations. While both INCB050465 and INCB052793 are P-gp substrates, their efflux transport via P-gp is likely to be saturated at the doses proposed for clinical evaluation, and thus further inhibition of P-gp should have no effect on INCB050465 or INCB052793 absorption. Therefore, a drug interaction between these compounds is unlikely in the setting of the proposed clinical study. Pharmacokinetics of INCB050465 and INCB052793 will be evaluated in subjects receiving both agents concurrently in Cohort H and compared with respective monotherapy data.

1.3.6.3. Clinical Summary of Combination Treatment With JAK1 Inhibition (Itacitinib [INCB039110]) and PI3Kδ Inhibition (INCB040093)

Study INCB 40093-102 is an ongoing, open-label, dose escalation, safety and tolerability study that has tested combination of another novel JAK1 inhibitor itacitinib and novel PI3Kδ inhibitor INCB040093. As of 21 JUL 2015, 55 subjects had received treatment with the combination. Generally treatment was well-tolerated. Grade ≥ 3 TEAEs occurring in > 1 subject were Pneumocystis *jiroveci* pneumonia (PJP; n = 5; 9.6%); hyponatremia and hypoxia (n = 3 each; 5.8%); and hypercalcemia and pneumonia (n = 2 each; 3.8%). Overall response rate in evaluable subjects who received INCB040093 + itacitinib combination therapy was 60.0% for HL and 27.3% for DLBCL. Additional details can be found in the INCB052793 IB.

1.4. Overview of Itacitinib (INCB039110)

Itacitinib adipate (INCB039110 adipate, referred to herein as itacitinib), is a novel, potent, and selective inhibitor of the JAK family of protein TYKs with selectivity for JAK1. Itacitinib is an investigational product that is proposed for development for treatment of MPNs, including myelofibrosis (MF); inflammatory diseases, including rheumatoid arthritis (RA) and psoriasis; graft-versus-host disease (GVHD); solid tumors; and B-cell malignancies.

1.4.1. Pharmacology of Itacitinib

Itacitinib potently inhibits JAK1 (half maximal inhibitory concentration [IC_{50}] = 3.6 nM at 1 mM adenosine triphosphate concentration), with 22- to > 500-fold selectivity over the other JAK family members, JAK2, JAK3, and TYK2. It does not significantly inhibit (< 30% inhibition) a broad panel of approximately 60 other kinases. Itacitinib is also potent (IC_{50} values of approximately 10 nM to 350 nM) in cytokine-driven cell-based assays. This effect is not due to general cytotoxicity. Itacitinib also inhibits the growth of the cytokine-dependent cell line INA-6. Itacitinib potently inhibits the phosphorylation of signal transducer and activator of STAT proteins and the production of proinflammatory factors induced by other cytokines, such

as IL-23 and IL-6, with IC_{50} values of approximately 30 nM to 100 nM. In contrast, itacitinib shows less inhibition in cell-based assays dependent on JAK2, with IC_{50} values of approximately 1 μM or greater, [redacted] In *in vivo* models of JAK-dependent malignancy, itacitinib impedes subcutaneous tumor growth of INA-6 cells expressing wild-type JAKs when administered by continuous infusion, achieving plasma concentrations well below those necessary to inhibit JAK2. Oral itacitinib also reduced splenomegaly in a model of JAK2 V617F-driven neoplasia relevant to MF.

Itacitinib did not demonstrate off-target activity or any activity in a number of non-JAK family kinases. In rat safety pharmacology studies, adverse findings, noted only at 1000 mg/kg, included a transient decrease in locomotor activity, a slight decrease in body temperature, and suppression of respiratory function. In a cardiovascular study in dogs, ≥ 60 mg/kg produced a potentially adverse lowering of arterial pressure, compensatory higher heart rate, and an increase in core body temperature; the no-observed-adverse-effects level (NOAEL) was 30 mg/kg. The IC_{50} for inhibition of the hERG channel was 65.3 μM.

Additional information can be found in the itacitinib IB.

1.4.2. Nonclinical Drug Metabolism and Pharmacokinetics of Itacitinib

In vitro and *in vivo* studies were conducted to characterize the absorption, distribution, metabolism, and excretion profile of itacitinib. In single-dose PK studies in rats, dogs, and monkeys, orally administered itacitinib was rapidly absorbed ($t_{max} \leq 2.0$ hours). Oral bioavailability was low in monkeys, moderate in dogs, and high in rats. After IV administration, itacitinib had a short half-life (≤ 1.2 hours) in all 3 species. Total systemic clearance was high in rats (100%) and low to moderate in dogs and monkeys (31%-37%). The Vd_{ss} in rats was greater than in dogs and monkeys, suggesting greater tissue distribution in rats. Itacitinib has minimal penetration across the blood-brain barrier in rats. Protein binding in plasma and serum from rats, dogs, and humans was moderate, and the fraction unbound was independent of itacitinib concentration.

In multiple-dose toxicokinetic studies in rats and dogs, the C_{max} and AUC values generally increased with dose. No sex differences were observed in dogs; however, plasma exposure in female rats was more than 2-fold higher than that of males. This difference was likely attributed to metabolism of itacitinib via male-specific CYP3A2. The mean C_{max} and AUC values were decreased after multiple-dose administration in rats, but the mechanism is unclear.

CYP3A4 is the major isozyme responsible for the metabolism of itacitinib in human liver microsomes. In a cultured human hepatocyte assay, itacitinib did not induce CYP1A2, CYP2B6, or CYP3A4/5 activity or mRNA levels, suggesting that the potential to induce P450 in clinical studies is low. *In vitro* assays indicated that itacitinib is a substrate of P glycoprotein and BCRP. In addition, the potential for itacitinib to cause clinical drug-drug interactions through CYP inhibition is low based on IC_{50} values.

In rats and dogs, excretion was rapid and complete after a single oral dose of ^{14}C-itacitinib. In rats, approximately 25%, 55%, and 20% of total radioactivity was excreted in urine, feces, and bile, respectively. In dogs, feces were the main elimination pathway (70%-80% of total recovered radioactivity), while urinary excretion accounted for < 20%. The major analyte

present in plasma and urine from all species studied was the parent compound. Itacitinib-derived radioactivity did not preferentially partition into the blood of rats and dogs.

In the rat quantitative whole-body autoradiography study, pigmented and nonpigmented male rats showed similar tissue distribution, except that concentrations in the pigmented eye uveal tract were substantially higher than in that of the nonpigmented rat, indicating an association of ^{14}C-itacitinib–derived radioactivity with melanin. The highest concentrations of radioactivity were found in the alimentary canal contents, bile, and urinary bladder contents, suggesting that biliary and renal excretion were both routes of elimination.

These data are further discussed in the itacitinib IB.

1.4.3. Potential Risks of Itacitinib Based on Preclinical Safety

Single oral doses of itacitinib up to 2000 mg/kg in rats and up to 1000 mg/kg in dogs produced no adverse effects. In multiple-dose studies in rats, dose-related body weight decreases and lower food consumption were noted. Pharmacology-related alterations in the multiple-dose rat studies included reversible lowering of white blood cell (WBC) count, reversible lymphoid depletion in lymphoid tissues, and reduction in bone marrow cellularity. The NOAEL in the 6-month rat study was 300 mg/kg per day. In dogs, GI inflammation was the DLT in multiple-dose studies of up to 3 months in duration. In the 6- and 9-month dog studies, generalized demodicosis, an effect secondary to the immunosuppressive effect of itacitinib, was the DLT. The NOAEL in the 9-month study was 10 mg/kg per day. When itacitinib was administered to pregnant rats and rabbits, fetotoxicity and fetal malformations and variations were observed at the highest dose levels tested; these effects were considered secondary to severe maternal toxicity at the same dose levels.

Genetic toxicity assessments, including a bacterial reverse mutation assay, *in vitro* chromosomal aberrations study in primary human peripheral blood lymphocytes, and *in vivo* micronucleus study in rats, indicate that itacitinib lacks potential for genotoxicity.

For additional information, refer to the itacitinib IB.

1.4.4. Clinical Summary of Itacitinib

Itacitinib is an investigational product that has been studied in subjects with underlying rheumatologic/inflammatory conditions, solid tumors, and hematologic malignancies. The explored doses ranged from 100 mg QD to 600 mg twice daily (BID). It is currently in development for the treatment of MPNs (including MF), GVHD, and solid and hematologic malignancies.

Adverse events that have been reported by more than 5% of healthy subjects receiving itacitinib in an individual study included fatigue, headache, neutropenia, nausea, contact dermatitis, ecchymosis, reticulocyte count decreased, excoriation, and nasal congestion. Adverse events reported by more than 10% of subjects in the MF study included anemia, fatigue, thrombocytopenia/platelet count decreased, upper respiratory tract infection, nausea, constipation, diarrhea, cough, peripheral edema, pyrexia, dyspnea, dizziness, pain in extremity, night sweats, abdominal pain, arthralgia, contusion, headache, pruritus, and vomiting. The only adverse event reported by more than 10% of itacitinib-treated subjects with an inflammatory

condition was nasopharyngitis in the psoriasis study; there were no TEAEs reported by more than 10% of subjects with RA.

Serious AEs (SAEs) reported in more than 1 subject in an individual monotherapy study included the following: pneumonia (5 MF subjects), anemia (5 MF subjects), pyrexia (2 MF subjects), congestive cardiac failure (3 MF subjects), leukocytosis (2 subjects), chest pain (2 MF subjects), acute renal failure (2 MF subjects), urinary tract infection (2 MF subjects), GI/upper GI hemorrhage (2 MF subjects), and hypotension (2 subjects).

No events of PJP have been reported in subjects receiving itacitinib monotherapy.

Itacitinib is also tested in combination with chemotherapy, PI3K delta inhibitors (INCB040093 and INCB050465) and as well as epacadostat (IDO-1 inhibitor), pembrolizumab, and corticosteroids.

Clinical experience with itacitinib as of 13 DEC 2016 is based on administration to 777 safety evaluable subjects. This includes 493 subjects who received itacitinib as a monotherapy, including healthy subjects (284) and subjects with MF (87), chronic plaque psoriasis (38), and RA (84). Also, 64 subjects with solid tumors received itacitinib in combination with chemotherapy; 78 subjects with lymphoid malignancies received itacitinib in combination with the PI3Kδ inhibitor, INCB040093; 38 subjects with solid tumors or lymphoid malignancies received itacitinib in combination with another PI3Kδ inhibitor, INCB050465; 35 subjects with solid tumors received itacitinib in combination with pembrolizumab, 40 subjects with solid tumors received itacitinib in combination with epacadostat; and 29 subjects with acute GVHD received itacitinib in combination with corticosteroids. Duration of exposure to itacitinib in subjects has reached up to approximately 209 weeks in subjects with MF. Chemotherapy combinations have been administered for up to 52 weeks; combination treatment with INCB040093 has been administered for up to 138 weeks; combination treatment with INCB050465 has been administered for up to 38 weeks; combination treatment with epacadostat has been administered for up to 32 weeks, combination treatment with pembrolizumab has been administered for up to 36 weeks; and combination treatment with corticosteroids has been administered for up to 40 weeks.

Serious AEs have been reported in subjects with solid tumors (33 subjects; 56.4%), lymphoid malignancies (43 subjects; 50.6%), MF (33 subjects; 37.9%), and RA (2 subjects; 2.4%).

As a result of itacitinib-mediated immunomodulation, an increased incidence of infections could possibly occur with itacitinib monotherapy. Strict clinical monitoring is indicated to identify and treat infections in study subjects should they occur.

Because of the potential for myelosuppression, subjects will have hematologic parameters closely monitored during initial clinical studies. If there are clinically relevant declines in hematology parameters, therapy may be interrupted until resolution or discontinuation. As itacitinib also has the potential to cause WBC margination (ie, a transient decrease in absolute neutrophil count), assessment of hematology parameters should be performed before study drug administration at all applicable study visits.

Itacitinib showed signs of efficacy in subjects with MF in monotherapy, as well as in combination with PI3K delta inhibitors in subjects with B-cell malignancies.

Additional information can be found in the itacitinib IB.

1.4.5. Clinical Pharmacokinetics of Itacitinib

Following a single dose of 300 mg itacitinib (3 × 100 mg tablets) in healthy volunteers, there was a 46% increase in C_{max} but only a 17% increase in total exposure ($AUC_{0-\infty}$) when administered with a medium-fat meal. The nonclinically significant impact on total exposure when administered with a medium-fat meal supported the administration of itacitinib without regard to food. A preliminary analysis comparing single doses of 100 mg (1 × 100 mg), 200 mg (2 × 100 mg), and 300 mg (3 × 100 mg; fasted) demonstrated that exposures increase in a greater-than-proportional manner.

Following multiple-dose administration of itacitinib 400 BID or 800 QD with a medium-fat meal, steady state was generally reached after 48 hours. Compared with Day 1, there was approximately 60% and 15% accumulation in $AUC_{0-\tau}$ for the 400 mg BID and 800 QD doses, respectively, following a medium-fat meal. The highest total daily exposure after multiple-dose administration was achieved after administration of 600 mg BID (29.0 μM·h [calculated as 2 × AUC_{0-12}]). Mean half-life of itacitinib is generally reported in the range of 3 to 9 hours with an overall mean of approximately 5 hours. After itacitinib 400 mg BID and 800 mg QD administration with a medium-fat meal, the intersubject CV% ranged from 25% to 34% for C_{max} and 23% to 40% for $AUC_{0-\tau}$.

Study INCB 39110-230 where itacitinib was administred in monotherapy orally as 100 mg BID, 200 mg BID, and 600 mg QD for up to 24 weeks to subject wih MF, the PK of itacitinib were characterized after multiple doses using the following sampling scheme: predose (Day 1 and Weeks 4, 12, and 24), and 1, 2, and 4 hours postdose (Weeks 4, 12, and 24). Itacitinib attained peak plasma concentrations with a median t_{max} of 2 to 4 hours. Steady state was achieved by Week 4. For increasing dose from 100 mg BID to 200 mg BID, itacitinib plasma exposures (C_{max} and AUC) appeared to be linear with regard to dose. Itacitinib exposures in subjects with primary or secondary MF were similar to those in healthy volunteers and subjects with stable, chronic plaque psoriasis. Refer to the itacitinib IB for more details.

1.5. Study Rationale

Several lines of evidence converge to support a significant role for JAK/STAT biology in the pathogenesis and clinical course of solid tumors and hematologic malignancies, and the hypothesis that JAK inhibition may be an effective therapeutic strategy in these diseases. Janus kinase/STAT activation has been shown to mediate tumor growth and survival, as well as resistance to chemotherapy in several tumor models, including pancreatic cancer (Catlett-Falcone et al 1999, Toyonaga et al 2003, Thoennissen et al 2009, Lesina et al 2011, Sansone and Bromberg 2012), MM (Burger et al 2009, Li et al 2010), and AML/MDS (Cook et al 2014, Spiekermann et al 2001).

The JAK/STAT pathway can become activated within pancreatic tumor cells either through mechanisms intrinsic to the cancer cells themselves (Fukushima et al 2003, Komazaki et al 2004, Fukuda et al 2011, Lesina et al 2011) or through complex stromal interaction with the tumor microenvironment (Bromberg and Wang 2009, Galm et al 2003). These interactions are mediated to a large extent through cytokine networks that either directly or indirectly signal through JAK/STAT dependent pathways. For example, paracrine sources of IL-6 from cancer-associated fibroblasts or myeloid cells can induce autocrine production of IL-6 and activation of STAT3 in tumor cells (Sansone and Bromberg 2012). Although precise mechanisms remain

unknown, it is clear that pancreatic cancer induces a systemic inflammatory response, possibly through inflammatory cytokine production by pancreatic tumor cells themselves (Bromberg and Wang 2009, Wigmore et al 2002) or by cytokines produced in the local inflammatory milieu (Protti and De Monte 2013). This systemic inflammatory response is largely mediated through JAK/STAT-dependent cytokine signaling and may contribute to local tumor growth. Perhaps more importantly, however, it may be a marker for the stromal inflammatory milieu in the tumor, and is itself associated with systemic manifestations such as the cachexia syndrome (Fearon et al 2013), which has independent prognostic significance in this disease. Thus, JAK/STAT signaling may contribute to the course of pancreatic cancer through tumor cell intrinsic mechanisms or through both the local and systemic effects of inflammatory cytokines. In turn, systemic inflammation may be directly involved in the systemic manifestations of the disease, such as cachexia, as well as a marker of JAK/STAT activation locally within the tumor.

Similarly, the interaction of MM cells with the microenvironment has been demonstrated to be crucial for the pathogenesis of MM and supports autocrine and paracrine signaling by a number of growth factors and cytokines, including IL-6. IL-6 and its soluble agonistic receptor, sIL-6R, are elevated in MM patients and have been associated with poor prognosis (Lauta 2003). Ligand binding results predominantly in activation of JAK1, leading to the phosphorylation of downstream effectors (eg, STATs). Additionally, in MM, epigenetic silencing of an autoregulatory feedback loop mediated by members of the SOCS (silencer of cytokine signaling) family has been documented in the majority of MM patients analyzed and is thought to contribute to a net increase in aberrant JAK-STAT pathway activation (Galm et al 2003). Hence, selective inhibition of JAK1 kinase activity in MM may provide therapeutic benefit to patients who currently do not have curative medicinal alternatives.

Preclinically, INCB052793 inhibited growth of the MM cell line, INA-6, with an IC_{50} of 238 ± 29 nM (n = 6), demonstrating that inhibition of JAK1 by INCB052793 abrogated the IL-6/JAK/STAT3 signaling pathway and induced cell death in the JAK/STAT-dependent INA-6 cell line. In addition, immune-compromised mice bearing well established subcutaneous INA-6 tumors that were dosed with INCB052793 demonstrated dose-dependent suppression of JAK/STAT signaling and a reduction in tumor growth.

Treatment outcomes in AML are poor. Despite various cytotoxic drug combinations and targeted therapies, disease recurrence is common. Cytokine stimulation induces proliferation and growth of AML blasts, and high levels of cytokines have been associated with poor prognosis in AML (Faderl et al 2005). The JAK/STAT pathway has been recognized as one of the most important signaling pathways downstream of cytokine receptors. Therefore, targeting this pathway with a JAK/STAT inhibitor may provide a way to influence the cytokine stimulation and proliferation of myeloid blast cells. Preclinical data published suggest that a JAK can inhibit AML cell proliferation by inhibiting STAT 3, 5 and induction of caspase-dependent apoptosis (Faderl et al 2005).

Subjects with high risk MDS who have failed prior therapy with hypomethylating agents (HMA) have no available standard of care. The median overall survival after azacitidine or decitabine failure in patients with MDS is 5.6 and 4.3 months respectively (Prébet et al 2011, Jabbour et al 2010, Duong et al 2013). The median OS of MDS subjects who developed secondary AML after azacitidine failure is 3.4 months (Prébet et al 2012).

Objective responses based on bone marrow and peripheral blood evaluation have been observed among subjects with AML/MDS who have previously failed treatment with HMA who were treated in Phase 1b part Cohort F (INCB052793 in combination with azacitidine). Based on unaudited data among 10 subject who who have previously failed treatment with HMA, 3 experienced complete marrow response without hematologic recovery. Of these, 2 were taken off study to undergo allogenetic transplantation. Another subject experienced reduction of bone marrow blasts from 70% to 10%. Therefore, in Phase 2 of this study, we will futher evaluate the efficacy and safety of INCB052793 and itacitinib in combination with azacitidine in this patient population. Testing 2 JAK1 inhibitors (INCB052793 and itacitinib) in 2 parallel cohorts will allow selection of the JAK1 inhitor that shows a more promising efficacy and safety in combination with azacitidine in this patient population.

1.6. Clinical Experience With INCB052793

As of the data cutoff date (19 JUN 2016), 34 subjects in Study INCB 52793-101 have received INCB052793 monotherapy (up to 100 mg QD), and 16 subjects have received INCB052793 (up to 35 mg QD) in combination with a standard-of-care anticancer agent (dexamethasone or azacitidine). INCB052793 has been administered in combination with dexamethasone to 6 subjects (Cohort B) with MM and in combination with azacitidine to 10 subjects (Cohort F) with AML or MDS. The median duration of treatment was 56 days for INCB052793 monotherapy and 57.5 days in combination with standard-of-care anticancer agents (dexamethasone or azacitidine).

Based on preliminary, unaudited data as of the data cutoff (19 JUN 2016), all subjects given INCB052793 monotherapy reported at least 1 TEAE. Three subjects (8.8%) given monotherapy had a fatal TEAE (respiratory failure for 2 subjects at 50 mg QD and a small intestinal obstruction for 1 subject at 75 mg QD). Ten subjects (29.4%) given INCB052793 monotherapy reported an SAE during the study; 5 of the SAEs (febrile neutropenia and platelet count decreased [observed at 50 mg QD], and dehydration, nausea, and vomiting for 1 subject at 100 mg QD) were considered by the investigator to be possibly treatment-related. Thrombocytopenia/platelet count decreased was the most frequently reported TEAE (44.1%) in subjects given INCB052793 monotherapy. Treatment-related TEAEs were reported for 70.6% of subjects given INCB052793 monotherapy; the most frequently reported treatment-related TEAE was thrombocytopenia/platelet count decreased (41.2%). Treatment-emergent AEs of Grade 3 or higher were noted in 58.8% of subjects given INCB052793 monotherapy; the most frequently reported ≥ Grade 3 TEAEs were hematologic or respiratory in nature. One subject given INCB052793 monotherapy discontinued treatment because of death caused by disease progression (with a fatal TEAE of respiratory failure), and 1 subject discontinued treatment because of multiple TEAEs.

For subjects given INCB052793 in combination with the standard-of-care anticancer agents, dexamethasone (Cohort B) or azacitidine (Cohort F), 1 subject in Cohort B and no subjects in Cohort F had a fatal TEAE (respiratory arrest) as of the data cutoff date. Eight subjects (50.0%) given combination therapy reported an SAE during the study; 4 of these subjects (25.0%; all in Cohort F [azacitidine]) reported SAEs of febrile neutropenia. All other SAEs in subjects given INCB052793 with a standard-of-care anticancer agent were noted in 1 subject each. Serious AEs of pneumonia and sepsis for 1 subject in Cohort B were considered by the investigator to be

possibly related to treatment with INCB052793 and dexamethasone. Fourteen subjects (87.5%) given INCB052793 with a standard-of-care anticancer agent reported at least 1 TEAE. The most frequently reported TEAEs (37.5%) were fatigue and injection site reaction. Other TEAEs reported in at least 20% of subjects were febrile neutropenia, thrombocytopenia/platelet count decreased, and oropharyngeal pain. Nine subjects (56.3%) given INCB052793 in combination with dexamethasone (Cohort B) or azacitidine (Cohort F) had TEAEs related to INCB052793 treatment. The most frequently reported INCB052793-related TEAEs in subjects given combination therapy were thrombocytopenia/platelet count decreased and fatigue (25.0% of subjects each). Other INCB052793-related TEAEs in ≥ 10% of subjects given combination therapy included neutropenia/neutrophil count decreased (18.8%) and alanine aminotransferase increased and aspartate aminotransferase (AST) increased (12.5% each). Ten subjects (62.5%) had TEAEs of Grade 3 or higher. The majority of ≥ Grade 3 TEAEs were hematologic in nature. Two subjects given INCB052793 in combination with a standard-of-care anticancer agent (both in Cohort F) discontinued treatment because of a TEAE. No subject given INCB052793 in combination with a standard-of-care anticancer agent discontinued treatment because of death. One subject in Cohort B (INCB052793 25 mg plus dexamethasone) had Grade 3 thrombocytopenia that was considered to be a DLT; this cohort has been expanded to 6 subjects. Among 10 subjects in Cohort F (INCB052793 plus azacitidine) at dose levels of 25 mg or 35 mg (5 subjects each), none had a DLT.

No clinically meaningful differences in safety have been observed since this data cutoff to date.

Preliminary, unaudited PK data show that, following multiple-dose oral administration, INCB052793 was absorbed rapidly and typically attained peak plasma concentrations within 0.5 to 2 hours after administration. INCB052793 exhibited low oral dose clearance, with mean clearance of 9.00 L/h and 14.4 L/h over the range from 15 mg QD to 100 mg QD. INCB052793 PK steady-state was attained before Day 8. The dose proportionality on steady-state exposure appeared to be observed over the range from 15 mg QD to 100 mg QD in Phase 1a. Coadministration of dexamethasone or azacitidine did not appear to affect the PK of INCB052793 when compared with 25 mg QD and 35 mg QD monotherapy.

1.7. Potential Risks and Benefits

1.7.1. Preclinical Safety

The toxicological profile of INCB052793 was characterized in single- and multiple-dose oral studies of up to 28 days in duration in rats and dogs, and in *in vitro* and *in vivo* genetic toxicology studies.

The most prominent findings following repeat-dose exposure in both rats and dogs consisted of lymphoid depletion of multiple lymphoid organs including lymph nodes, spleen, thymus, bronchus-associated lymphoid tissue (BALT), and gut-associated lymphoid tissue (GALT). The incidence and severity of these findings were dose-related. Reduced bone marrow cellularity, with an associated increase in adipocyte population, was also observed to be dose-dependent in incidence and severity. Clinical pathology, immunophenotyping, and bone marrow cytology evaluations revealed alterations that were generally reflective of the pharmacological effects of INCB052793 on lymphoid organs.

Effects secondary to immunosuppression led to the death of 1 female dog given INCB052793 at 15 mg/kg per day (primary cause of death was bronchioloalveolar inflammation with bacterial colonization) and 1 male rat given INCB052793 at 75 mg/kg per day (cause of death was pyelonephritis with bacterial colonization). An additional male rat given 75 mg/kg per day was found dead; although the cause of death was not clear, severe lymphoid system changes likely contributed to the death of this animal. Skin ulceration of the cervical region was noted in female rats given ≥ 15 mg/kg per day and male rats given 75 mg/kg per day. These lesions may have initiated from rats rubbing their necks on their feeding containers, and sustained immunosuppression resulting from INCB052793 administration likely exacerbated this lesion. This lesion appeared recoverable. A lowering of red cell mass and circulating reticulocyte count, coupled with a slight reduction in the erythroid component of the bone marrow (dogs only), may be reflective of JAK2 inhibition. Although all of the aforementioned findings were primary or secondary pharmacological effects, these findings were considered to be adverse (excessive) based on both severity and incidence (rats given 75 mg/kg per day) or based on the adverse nature of the effects secondary to JAK inhibition (dogs given 15 mg/kg per day).

There was no evidence of off-target toxicity of INCB052793 in dogs. In rats, reversible minimal-to-mild hyperostosis was observed in animals given 75 mg/kg per day. Ovarian hemorrhage and luteal cysts were noted in female rats given ≥ 15 mg/kg per day, and a single female given 5 mg/kg per day had mild corpus luteal hemorrhage. Ovarian changes persisted through the recovery period.

According to the algorithms described in ICH S9 Guidance for Industry (ICH 2010), the starting clinical dose for small molecules is often set at 1/10 the severely toxic dose in 10% of the animals (STD10) in rodents, or 1/6 the highest non-severely toxic dose (HNSTD) in non-rodents. INCB052793 is pharmacologically active in both rats and dogs. Because adverse findings in both rats and dogs were primarily related to pharmacological effects on the lymphoid system, both species are appropriate for consideration of the starting clinical dose. Based on the 28-day study in rats, severe toxicity was observed at 75 mg/kg per day; therefore, this dose level was considered to approximate the rat STD10. The human equivalent dose associated with 75 mg/kg per day based on standard body surface area conversion is 720 mg, and 1/10 this dose is 72 mg. In the 28-day dog study, the HNSTD was considered to be 5 mg/kg per day based on the severity of lymphoid depletion at higher doses and secondary effects leading to early euthanasia of 1 female dog given 15 mg/kg per day. The human equivalent dose associated with 5 mg/kg per day is 162 mg; 1/6th of this dose is 27 mg.

INCB052793 was not mutagenic in a bacterial mutagenicity assay. INCB052793 was not clastogenic in the presence or absence of S9 metabolic activation in an in vitro chromosome aberration assay in human peripheral blood lymphocytes, however numerical aberrations were noted in both the absence and presence of S9 in this assay. An increase in micronuclei in bone marrow of rats administered high doses of INCB052793 together with the polyploidy response noted in the chromosome aberration assay suggests that INCB052793 is aneugenic (an aneugen is an agent that affects cell division and the mitotic spindle apparatus resulting in the loss or gain of whole chromosomes).

For potential risks of itacitinib based on preclinical studies, see Section 1.4.3 and the itacitinib IB.

1.7.2. Potential Risks Related to INCB052793 and Itacitanib

In repeat-dose studies in both rat and dog, reversible decreases in circulating lymphocytes and/or reticulocytes and red cell mass parameters were observed. Microscopically, reversible decreases in lymphocytes in various lymphoid organs and hypocellularity of the bone marrow have been described. The changes seen in red cell mass parameters are likely due to JAK2 inhibition at the higher doses used in toxicology studies. The incidence and severity of these histologic findings were considered adverse at the highest dose of 75 mg/kg per day evaluated in the 28-day rat study. In the 28-day dog study, 15 mg/kg per day was considered to be an adverse dose level based on the severity of secondary pharmacological effects. Effects on the lymphoid organs and bone marrow are expected based on the mechanism of action of INCB052793. Reversibility of the pharmacological effects has been demonstrated pre-clinically, and would be expected to occur in a clinical setting.

All subjects will have hematologic parameters closely monitored during the study. Therapy will be withdrawn or dosing interrupted until resolution if there are clinically relevant declines in hematology parameters. Dose-modification criteria in regards to changes in hematologic parameters are specified in Table 1.

Off-target toxicities were noted in the 28-day rat study and included ovarian hemorrhage and luteal cysts in females given ≥ 15 mg/kg per day. It should be emphasized that the corpora lutea are nonfunctional at the time of luteolysis, the point at which the cysts appear to be forming. The appearance of large numbers of normal-appearing ovarian follicles with all stages of ovum development represented suggests that reproductive function is not impacted by INCB052793 treatment. Therefore, this finding is not expected to pose a risk to women of childbearing potential.

Reversible minimal-to-mild hyperostosis in the distal femoral metaphysis was observed in rats given 75 mg/kg per day. This lesion was not observed in any animals given 5 or 15 mg/kg per day. The rat ovarian and bone findings are not expected to pose a risk to humans as the plasma exposures associated with a dose of 75 mg/kg per day, where hyperostosis and a high incidence of ovarian perturbations occurred, are 20- and 33-fold greater in males and females, respectively, than the projected human exposure at a maximum proposed dose of 150 mg QD.

An increase in micronuclei in bone marrow of rats administered INCB052793 at 1000 and 2000 mg/kg, together with the polyploidy response noted in the chromosome aberration assay, suggests that INCB052793 is aneugenic. In contrast to mutagens, aneugens typically exhibit a threshold response (Bentley et al 2000, Henderson et al 2000); therefore, an estimation of risk can be obtained from calculation of a safety margin. In the rat micronucleus study, a dose level of 500 mg/kg did not produce micronuclei, and at this dose level the plasma exposure is 85-fold greater than the estimated exposure at a maximum dose level of 150 mg INCB052793 to be studied in humans. Therefore, based on the collective evidence, INCB052793 is not expected to present a genotoxic risk to humans at the intended dose levels in this study.

Additional information can be found in the INCB052793 IB.

Potential risks related to itacitinib are discussed in Section 1.4.4 and the itacitinib IB.

1.7.3. Risks Related to Standard-of-Care Agents

1.7.3.1. Gemcitabine

Myelosuppression is the principal DLT with gemcitabine therapy. Gemcitabine can suppress bone marrow function as manifested by leukopenia, thrombocytopenia, and anemia, and myelosuppression is usually the DLT in clinical studies. Subjects should be monitored for myelosuppression during therapy. Dose adjustments for hematologic toxicity are frequently needed. The most common adverse reactions for single-agent (≥ 20%) gemcitabine are nausea and vomiting; anemia; increased ALT, AST, and ALP; neutropenia; leukopenia; proteinuria; fever; hematuria; rash; thrombocytopenia; and dyspnea. Prolongation of the infusion time beyond 60 minutes and more frequent dosing, compared to weekly dosing, has been shown to increase toxicity. A complete discussion of risks associated with gemcitabine can be found at http://dailymed.nlm.nih.gov/.

1.7.3.2. *nab*-Paclitaxel

Myelosuppression is the principal DLT with *nab*-paclitaxel therapy. *nab*-Paclitaxel can suppress bone marrow function, as manifested by leukopenia, thrombocytopenia, and anemia, and myelosuppression is usually the DLT in clinical studies. Subjects should be monitored for myelosuppression during therapy. Dose adjustments for hematologic toxicity are frequently needed. The most common adverse reactions for single-agent (≥ 20%) *nab*-paclitaxel are neutropenia, peripheral neuropathy, infections, and electrocardiogram (ECG) abnormalities. A complete discussion of risks associated with *nab*-paclitaxel can be found at http://dailymed.nlm.nih.gov/.

1.7.3.3. Dexamethasone

The most common adverse reactions associated with the use of dexamethasone include insomnia, fluid retention, weight gain, dyspepsia, impaired wound healing, and hyperglycemia. Less common adverse reactions include opportunistic infection or viral reactivation secondary to immunosuppression, mood instability, depression, hypokalemia, hypertension, rash, lightheadedness, headache, and hot flashes. Severe adverse effects are typically managed through interruption of dexamethasone dosing and supportive measures. A complete discussion of risks associated with dexamethasone can be found at http://dailymed.nlm.nih.gov/.

1.7.3.4. Carfilzomib

The principal DLT associated with the use of carfilzomib is thrombocytopenia, with a reported overall incidence of 36%; Grade 4 thrombocytopenia has been reported in 10% of subjects across several clinical studies. Subjects will be monitored for platelet count before each dose of carfilzomib. Other hematologic AEs that have been reported at a ≥ 20% overall incidence include anemia, lymphopenia, and neutropenia, with a Grade 3 or 4 incidence of 22.4%, 18.1%, and 11.3%, respectively. Common nonhematologic toxicities reported at an overall incidence of ≥ 20% include fatigue, nausea, dyspnea, cough, headache, increased creatinine, peripheral edema, upper respiratory infection, vomiting, constipation, and back pain. Use of carfilzomib has also been associated with tumor lysis syndrome and infusion reactions. Premedication with dexamethasone and hydration before dosing will be required, consistent with the

recommendations in the product label. A complete discussion of risks associated with dexamethasone can be found at http://dailymed.nlm.nih.gov/.

1.7.3.5. Bortezomib

The principal dose limiting adverse reaction associated with the use of bortezomib is sensory peripheral neuropathy, which is typically characterized by a burning sensation, paresthesias, numbness, and/or neuropathic pain. Peripheral neuropathy of Grade 1 or higher is observed in ≥ 30% of patients taking bortezomib. It is often reversible in the majority of patients after treatment withdrawal and/or dose reduction. Subjects will be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, paresthesia, discomfort, neuropathic pain, or weakness. Thrombocytopenia has been observed in ≥ 30% of patients, with a 5% incidence of Grade 4 thrombocytopenia. Clinical studies have reported platelet count nadir levels of 40% of baseline. Other common adverse reactions associated with the use of bortezomib (≥ 20%) are asthenic conditions, nausea, diarrhea, constipation, appetite decreased, pyrexia, vomiting, and anemia. A complete discussion of risks associated with bortezomib can be found at http://dailymed.nlm.nih.gov/.

1.7.3.6. Lenalidomide

Myelosuppression is the primary DLT observed with lenalidomide therapy, typically manifesting as thrombocytopenia and/or neutropenia. Hematologic toxicities are reversible and are managed through dose interruptions and/or reductions. The rate of thrombocytopenia and neutropenia have each been reported at a ≥ 30% incidence in clinical studies. Subjects will have blood counts monitored weekly during the first cycle of treatment and no less than monthly thereafter. Use of lenalidomide is also associated with venous thromboembolic events, with a reported deep vein thrombosis and pulmonary embolism rate of 7.4% and 3.7%, respectively. Thromboprophylaxis will be instituted as indicated. Other common adverse reactions associated with the use of lenalidomide (≥ 20%) in patients with MM include fatigue, constipation, rash, pyrexia, anemia, peripheral edema, and nausea. Lenalidomide is an analogue of thalidomide, which a known teratogen. Preclinical studies of lenalidomide have also revealed teratogenic properties in monkeys; thus, use during pregnancy is contraindicated. A complete discussion of risks associated with lenalidomide can be found at http://dailymed.nlm.nih.gov/.

1.7.3.7. Pomalidomide

Myelosuppression is the primary risk associated with pomalidomide therapy, typically manifesting as neutropenia (53% overall) and anemia (38% overall); thrombocytopenia (26% overall) is observed less frequently than other hematologic toxicities. Subjects will have blood counts monitored weekly during the first cycle of treatment and biweekly thereafter. Consistent with other agents in this class, use of pomalidomide is also associated with venous thromboembolic events, with a reported deep vein thrombosis and pulmonary embolism rate of approximately 3%. Thromboprophylaxis will be instituted as indicated by the pomalidomide package insert (Pomalyst 2015). Other common adverse reactions associated with the use of pomalidomide (≥ 30%) in patients with MM include fatigue, constipation, diarrhea, nausea, asthenia, back pain, upper respiratory tract infection, and dyspnea. Pomalidomide is an analogue of thalidomide, which a known teratogen; thus, use during pregnancy is contraindicated. Refer to the Pomalyst® US package insert (Pomalyst 2015) for additional details.

1.7.3.8. 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 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/.

1.7.4. Potential Risks of Combination Therapy of INCB052793 and INCB050465

Incyte is proposing to study 2 investigational drugs, INCB052793 and INCB050465, in combination for the treatment of relapsed/refractory lymphomas. The principle toxicity of inhibiting both PI3Kδ and JAK1 pathways is expected to be reversible effects on immune function. Combined inhibition may adversely affect both B-cell and T-cell immune function with resultant increased risk of a variety of infections. Subjects will be closely monitored for bacterial infections, viral reactivation, and opportunistic infections, and treatment will be interrupted for infections that can be easily managed with antibiotic therapy and discontinued for infections that are serious or require prolonged antibiotic therapy.

Study INCB 40093-102 is combining another PI3Kδ inhibitor, INCB040093, with the JAK1 inhibitor itacitinib (see Section 1.3.6.1). Five cases of PJP have been reported by subjects receiving this combination therapy. Therefore, all subjects receiving combination therapy with INCB052793 and INCB050465 in this study must receive PJP prophylaxis. Serum (1,3)-β-D-glucan will be monitored each cycle throughout the study and approximately 3 months after discontinuation of the combination as a tool for early diagnosis of PJP. If serum (1,3)-β-D is > 80 pg/mL, correlation should be made with clinical and radiological findings. Infectious disease consultation may be obtained, and the subject should be managed according to the local guidelines for suspected cases of PJP. If PJP is confirmed, the subject should be discontinued from the study and managed according to local guidelines. Viral reactivation (ie, shingles) was also observed in subjects receiving INCB040093 monotherapy and combination therapy with itacitinib.

Effects on white blood cell, red blood cell, and platelet counts could result from JAK1 inhibition and result in infections, anemia, or thrombocytopenia requiring transfusions, which may be more likely in subjects with lymphomas that are refractory to recent therapy or transplantation.

INCB050465 has been shown to affect hematologic parameters; however, cytopenias are not expected to be worse with combination PI3Kδ and JAK1 inhibition. In the study combining itacitinib with INCB040093, anemia has occurred in 14.3% of subjects receiving INCB040093 monotherapy and 16.4% of subjects receiving combination therapy. Neutropenia has occurred in 18.4% of subjects receiving monotherapy and 27.3% of subjects receiving combination therapy; thrombocytopenia was reported in 4.1% of subjects receiving INCB040093 monotherapy compared with an incidence of 36.4% of subjects receiving combination therapy.

Idelalisib is another PI3Kδ inhibitor approved by the FDA in July 2014 for treatment of relapsed/refractory follicular lymphoma and relapsed small lymphocytic lymphoma and for treatment of CLL in combination with rituximab. Severe toxicities seen with the use of this agent include hepatotoxicity (fatal or serious occurring in 14%), fatal and/or serious diarrhea or colitis (14%), intestinal perforation, and pneumonitis. Based on experience with idelalisib and INCB040093, hepatotoxicity is a risk with this class of agents. Preclinically, hepatotoxicity with INCB050465 was only seen at plasma exposures > 65-fold higher than the projected clinical exposure at 10 mg QD. The pharmacophore of INCB050465 is different from both idelalisib and INCB040093, which are similar to each other.

1.7.5. Risks Related to the Combination Regimens

These medications individually or in combination may impact the function of the bone marrow, particularly the development of neutropenia, anemia, and thrombocytopenia in a dose-dependent manner. The pharmacologically targeted doses of INCB052793 and itacitinib that will be used in this study are not expected to result in a substantial myelosuppressive effect; however, the risks of concomitant INCB052793, itacitinib, and other agents that induce myelosuppression are unknown. Hematology parameters will be closely monitored in all study subjects and are expected to be reversible. In addition, all AEs will be monitored to identify occurrences of new safety signals, or potentiation of any side effects that may overlap with the side effects that are intrinsic to the standard-of-care agent being used. As indicated in Sections 1.2, 1.3, and 1.4, the risk of a metabolic drug interaction between INCB052793, itacitinib, and the proposed combination agents is low.

1.7.6. INCB052793 and Itacitinib Potential Benefits

INCB052793 represents a novel, potent compound with approximately 100-fold selectivity for JAK1 versus other JAKs, whereas itacitinib, another potent compound, inhibits JAK1 with 22-to > 500-fold selectivity over the other JAK family members. Because JAKs have been shown to be activated in many malignancies, inhibition may provide a method to treat these diseases either alone or in combination with chemotherapeutics or other targeted therapies. The degree of JAK1 inhibition that is being targeted in the current study may result in clinical benefit.

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

Oral drug administration is generally the most convenient and cost-effective method of drug delivery for medications requiring continuous exposure. In Phase 1a, one cycle will be defined as 21 continuous days of treatment; treatment for subjects will consist of repeating 21-day cycles. In Phase 1b and Phase 2, 1 cycle will be defined as 21 continuous days (Phase 1b Cohorts D and H) or 28 continuous days (Phase 1b Cohorts A, B, C, E, F, and G; Phase 2 Cohorts I and J) of treatment; treatment for subjects will consist of repeating 21- or 28-day cycles, appropriate to the treatment arm.

In Phase 1a Part 1, the dose sequence will be a repeated ascending dose design intended to obtain safety, tolerability, PK, [redacted] information for INCB052793 following multiple doses in subjects. The initial starting dose for Phase 1a Part 1 of this study will be 25 mg QD, which is based on review of preclinical safety and toxicology studies. If warranted, lower dose levels may be explored during Part 1 to further evaluate the safety, PK, [redacted] profile of INCB052793.

The DLTs seen in the preclinical studies are reversible with cessation of dosing, and subjects will be closely monitored for potential safety signals. Previous experience with JAK inhibitors has shown that the neutropenic and thrombocytopenic toxicities are usually apparent during the first 2 weeks of study drug administration. Based on this information, a 21-day (Phase 1a and Phase 1b/Cohorts D and H) to 28-day (Phase 1b/ Cohort A, B, C, E, F, and G) cycle will provide an adequate time frame for evaluation of DLTs and determination of the maximum tolerated dose (MTD). In addition, safety will be closely monitored beyond the 21-day and 28-day cycles and throughout the study.

In Phase 1b/Cohort A, the *nab*-paclitaxel/gemcitabine regimen chosen for this study is appropriate to the patient population and is consistent with established guidelines (Masamune et al 2005, Mehta 2010, NCCN Guidelines) in which 125 mg/m^2 and 1000 mg/m^2, respectively, every week for 3 weeks every 28 days has been shown to be generally both tolerated and effective. The recently completed Phase 3 study of the safety and efficacy of *nab*-paclitaxel/gemcitabine combination in pancreatic cancer (Von Hoff et al 2013) indicated that dose reductions of *nab*-paclitaxel (41%) and gemcitabine (47%) may be clinically indicated.

In Phase 1b/Cohort B, the dexamethasone dose and frequency selected for use in this study is consistent with those evaluated in other clinical studies (Rajkumar et al 2010, Richardson et al 2014a), in which dexamethasone was administered in combination with 1 or more antimyeloma agents.

In Phase 1b/Cohort C, the carfilzomib regimen selected for use in this study (20 mg/m^2 IV on Days 1 and 2 followed by 27 mg/m^2 IV on Days 8, 9, 15, and 16 of Cycle 1 and for all doses of each 28-day cycle thereafter) is appropriate to the patient population and has found to be tolerable and active both as a single agent (Alsina et al 2012) and in combination with other agents (Stewart et al 2015).

In Phase 1b/Cohort D, the bortezomib regimen is appropriate to the patient population and consistent with the product label (Velcade 2014) and established guidelines (NCCN Guidelines) of 1.3 mg/m^2 IV or subcutaneously (SC) on Days 1, 4, 8, and 11 of each 21-day treatment cycle.

In Phase 1b/Cohort E, the starting lenalidomide dose level and frequency are appropriate to the patient population and consistent with the product label (Revlimid 2015) and established guidelines (NCCN Guidelines) in which 25 mg administered orally QD on Days 1 through 21 of each 28-day cycle has been shown to be and effective and generally tolerated.

In Phase 1b/Cohort F, the azacitidine regimen selected for use in this study (75 mg/m^2 SC for 5 days, followed by 2 days of no treatment, then 75 mg/m^2 for 2 days of each 28-day treatment cycle) is appropriate to the patient population. The tolerability and activity of this regimen has 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.

In Phase 1b/Cohort G, the doses of pomalidomide (4 mg PO on Days 1 to 21 of each 28-day cycle) and dexamethasone (40 mg once per day PO on Days 1, 8, 15, and 22 of a 28-day cycle) are the recommended doses in the pomalidomide label (Pomalyst 2015).

In Phase 1b/Cohort H, the initial dose level of INCB050465 is 20 mg QD. This dose level has been evaluated in the ongoing INCB 50465-101 study (Section 1.3) and has been determined to

be safe in a dose escalation cohort including 4 subjects; dose levels up to 30 mg QD since have been evaluated with no DLTs observed to date at any dose level.

In Phase 2/Cohort I, the dose of INCB052793 used in combination with azacitidine is 35 mg QD. For the selected azacitibine regimen, refer to the Phase 1b/Cohort F above.

In Phase 2/Cohort J, the dose of itacitinib used in combination with azacitidine is 300 mg QD. The first 3 to 6 subjects enrolled in this cohort will be monitored for occurrence of DLTs before enrolment of more subjects. If this dose exceeds the MTD, new subjects will be enrolled at 200 mg QD and monitored as above.

For the selected azacitibine regimen, refer to the Phase 1b/Cohort F above.

Doses of INCB052793 selected for evaluation in Phase 1b will be based on the safety established in Phase 1a, and likewise the dose selected for evaluation in Phase 2 will be based on safety and signs of efficacy established in Phase 1b. For the treatment of advanced malignancies, the maximum individually tolerated dose of INCB052793 that spares inhibition of JAK2 should provide the best chance of efficacy while minimizing the potential for side effects (eg, myelosuppression).

The itacitinib dose is based on the favorable efficacy and tolerability observed at that dose level in several studies. Details can be found in the itacitinib IB.

The Phase 1a portion of the study will continue to assess INCB052793 safety, PK, [redacted] and antitumor activities to explore the therapeutic index of INCB052793 monotherapy and establish range of PADs for the combination portion. The intention is provide patients with unmet medical need with more efficacious treatment but not incur added toxicities.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objectives

- Phase 1a: To assess the safety and tolerability of INCB052793 in subjects with advanced malignancies and select doses for further evaluation.
- Phase 1b: To assess the safety and tolerability of INCB052793 in combination with standard therapies and the novel PI3Kδ inhibitor INCB050465 in subjects with advanced malignancies.
- Phase 2: To evaluate the efficacy of INCB052793 in combination with azacitidine and of itacitinib in combination with azacitidine in subjects with AML and high-risk MDS who have failed prior therapy with HMA, based on ORR.

2.2. Secondary Objectives

- To assess preliminary efficacy by assessing the ORR in subjects with advanced malignancies.
- To assess the safety and tolerability of INCB052793 in combination in azacitidine and of itacitinib in combination with azacitidine in subjects with AML and high-risk MDS who have failed prior therapy with HMA.
- To assess the PK of INCB052793 as monotherapy administered in the fasted state and the effect of food on the PK of INCB052793.
- To assess the PK of INCB052793 when administered in combination with standard therapies and INCB050465 in subjects with advanced malignancies, to assess the PK of INCB050465 when administered in combination with INCB052793, and to assess the PK of itacitinib when administered in combination with azacitidine.

3. SUBJECT ELIGIBILITY

3.1. Study Population

Individuals diagnosed with histologically or cytologically confirmed malignancies specified below will be enrolled in the study.

Phase 1a Monotherapy: In Part 1 dose escalation and Part 2 dose expansion, subjects diagnosed with an advanced malignancy who have failed or are refractory to available treatments will be enrolled.

Phase 1b Combination Therapy: Subjects diagnosed with advanced or metastatic solid tumors, limited to pancreatic adenocarcinoma (first or second line), triple-negative breast cancer (second line), or urothelial cancer (second line; Cohort A); relapsed or refractory MM (Cohorts B, C, D, E, and G); AML/MDS (Cohort F); or lymphoma (Cohort H) will be enrolled.

Phase 2: Subjects diagnosed with AML and high-risk MDS subjects who failed prior therapy with HMA.

3.2. Subject Inclusion Criteria for Phase 1a Monotherapy

The following criteria are required for inclusion in Phase 1a of the study:

1. Age 18 years or older.
2. Histologically or cytologically confirmed solid tumor (TGA) or hematologic malignancy (TGB). For Part 2 expansion, measurable or evaluable disease is required.
3. Life expectancy of 12 weeks or longer.
4. Must have received ≥ 1 prior treatment regimen and currently demonstrating progressive disease.
5. Must not be a candidate for potentially curative or standard-of-care approved therapy.
6. Female subjects of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy, and are not postmenopausal, defined as ≥ 12 months of amenorrhea) must have a negative serum pregnancy test at screening. All female subjects of childbearing potential must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through follow-up. (Note: Permitted methods that are at least 99% effective in preventing pregnancy [see Appendix A] should be communicated to the subjects and their understanding confirmed).
7. Men must agree to take appropriate precautions to avoid fathering a child (with at least 99% certainty) from screening through follow-up. (Note: Permitted methods that are at least 99% effective in preventing pregnancy [Appendix A] should be communicated to the subjects and their understanding confirmed.)
8. Ability to comprehend and willingness to provide informed consent.

3.3. Subject Inclusion Criteria for Phase 1b and Phase 2 Combination Therapy

The following criteria are required for inclusion in Phase 1b and Phase 2 of the study:

1. Age 18 years or older.
2. Phase 1b:

   Cohort A: Histologically or cytologically confirmed pancreatic adenocarcinoma, triple-negative breast cancer, or urothelial cancer with at least 1 measurable or evaluable target lesion.

   Cohorts B, C, D, E, and G: Histologically confirmed MM and measureable/evaluable disease as defined by 1 or more of the following:

   - Serum M-protein ≥ 0.5 g/dL.
   - Urine M-protein ≥ 200 mg/24 hours.
   - Serum free light chain (FLC): involved FLC level ≥ 10 mg/dL provided serum FLC ratio is abnormal.

   Cohort F: Confirmed AML or MDS (International Prognostic Scoring System intermediate-1, intermediate-2, or high-risk) or MDS/myeloproliferative neoplasms (MPN) overlap syndromes in accordance with WHO diagnostic criteria, including chronic myelomonocytic leukemia (CMML), atypical BCR-ABL1–negative chronic myeloid leukemia, MDS/MPN unclassifiable, and named refractory anemia with ring sideroblasts and thrombocytosis.

   Cohort H: Individuals diagnosed with lymphoma.

   - Subjects must not currently be a candidate for potentially curative hematopoietic stem-cell transplant and/or high-intensity chemotherapy.

   Phase 2:

   Cohorts I and J:

   - Confirmed AML or high-risk MDS (International Prognostic Scoring System -2, or high risk) in accordance with WHO diagnostic criteria.
3. Life expectancy of 12 weeks or longer.
4. Prior therapy Phase 1b:

   Cohort A: No more than 1 prior chemotherapy regimen for advanced or metastatic disease (not including neoadjuvant and/or adjuvant therapy).

   - There is no restriction on the number of prior nonmyelosuppressive targeted therapies; targeted therapy alone will not be considered chemotherapy for the purposes of this study.

   Cohorts B, C, D, E, and G: Must have relapsed from or have been refractory to ≥ 2 prior treatment regimens, including a proteasome inhibitor and an immunomodulatory drug (IMiD).

Cohort F: May have received any number of prior treatment regimens or be treatment-naive.

Cohort H: Must have relapsed from or have been refractory to available treatments.

- Subjects who have previously been discontinued from the standard-of-care agent (Cohorts A-G) or PI3Kδ inhibitors (Cohort H) being used in a specific cohort due to toxicity or intolerance may not enroll in that cohort (eg, subjects previously intolerant to bortezomib may not enroll in Cohort D).

Prior therapy Phase 2:

Cohorts I and J: Must have failed prior therapy with HMA. Failure of prior therapy with HMA is defined as one of the below:

- progression to AML
- 50% increase in bone marrow blasts.
- relapsed disease after response
- at least 4 cycles of treatment without clinical benefit (hematologic improvement [HI] or better)

5. Female subjects of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy, and are not postmenopausal, defined as ≥ 12 months of amenorrhea) must have a negative serum pregnancy test at screening (additional requirements for Cohort E are specified in Table 13). All female subjects of childbearing potential must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through follow-up if of childbearing potential. (Note: Permitted methods that are at least 99% effective in preventing pregnancy [see Appendix A] should be communicated to the subjects and their understanding confirmed).
6. Men must agree to take appropriate precautions to avoid fathering a child (with at least 99% certainty) from screening through follow-up. (Note: Permitted methods that are at least 99% effective in preventing pregnancy [Appendix A] should be communicated to the subjects and their understanding confirmed.)
7. Ability to comprehend and willingness to provide informed consent.

3.4. Subject Exclusion Criteria for Phase 1a, Phase 1b, and Phase 2

If met, any of the following criteria will lead to subject exclusion from the study:

1. Current pregnancy or breastfeeding.
2. Prior receipt of a selective JAK1 inhibitor (Phase 1a only; prior receipt of ruxolitinib is permitted.
3. Known hypersensitivity to any of the active substances or any of their excipients, including INCB052793, INCB050465, gemcitabine, *nab*-paclitaxel, dexamethasone, carfilzomib, bortezomib, lenalidomide, or azacitidine (Phase 1b and Phase 2 only, as appropriate to treatment cohort).

4. Received an investigational study drug within 28 days or 5 half-lives (whichever is longer) before receiving their first dose of study drug, except if approved by the sponsor's medical monitor.
5. Any approved anticancer medications within 21 days or 5 half-lives (whichever is longer) before receiving the first dose of study drug (42 days for nitrosoureas) or with medical monitor approval EXCEPT steroids at ≤ 10 mg prednisone daily (or equivalent; steroid exception does not apply to Phase 1b/Cohort B or G) and hydroxyurea to control blood counts.
6. Any unresolved toxicity ≥ Grade 2 (except stable Grade 2 peripheral neuropathy and alopecia) from previous anticancer therapy.
   - Phase 1b/Cohort D may not have > Grade 1 peripheral neuropathy at baseline.
7. Known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks before the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and have not required steroids for at least 7 days before study treatment.
8. Eastern Cooperative Oncology Group (ECOG) performance status > 2.
9. Any of the following laboratory results at screening without transfusions and hematopoietic growth factor support (except Phase 1b/Cohort F and Phase 2/Cohorts I and J):

Laboratory Parameter	Phase 1a/TGA and Phase 1b/Cohort A	Phase 1a/TGB and Phase 1b/Cohorts B Through H Except F
Hemoglobin (g/dL)	< 10.0	< 8.0
Platelet count (10^9/L)	< 100	< 75
Absolute neutrophil count (10^9/L)	< 1.5	< 1.0

   - No specific hematologic exclusion criteria apply to Phase 1b/Cohort F and Phase 2/Cohorts I and J
10. Any of the following laboratory results at screening irrespective of causality, except if approved by the sponsor:
    - Conjugated bilirubin > 1.2 × upper limit of normal (ULN; need only be tested if total bilirubin exceeds > 1.5 × ULN). In Phase 2, Cohorts I and J, Stage 2: total bilirubin > 3 × ULN.
    - Alkaline phosphatase > 2.5 × ULN (or > 5 × ULN if bone metastases are present and hepatic parenchymal metastases are absent).
    - AST or ALT > 3.0 × ULN (> 2.0 × ULN for Phase 1a/Part 1 and Phase 1b/Part 1). In Phase 2, Cohorts I and J, Stage 2: subjects with any AST value.
    - Creatinine clearance of < 60 mL/min (30 mL/min for subjects with MM and subjects in Phase 2, Cohorts I and J, Stage 2) measured or calculated by Cockroft-

Gault equation or estimated GFR < 60 mL/min/1.73 m^2 (30 mL/min/1.73 m^2 for subjects with MM and subjects in Phase 2, Cohorts I and J, Stage 2) using the Modification of Diet in Renal Disease (MDRD) formula.

11. Known human immunodeficiency virus infection.
12. Evidence of HBV or HCV infection or risk of reactivation. Subject cannot be positive for HBV DNA, HCV RNA, hepatitis B surface antigen, or anti–hepatitis B core antibody, except if approved by the medical monitor.
13. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTcF interval > 450 milliseconds (> 480 msec for subjects in Phase 2, Cohorts I and J, Stage 2) is excluded.
14. History of major stomach or intestinal surgery, or malabsorption syndrome (eg, Crohn's or chronic pancreatitis) that would, by clinical judgment, affect the absorption of study drug.
15. Use of any potent CYP3A4 inhibitor (see Appendix C) within 14 days or 5 half-lives (whichever is longer) of the first study drug.
16. Any known contraindications to the use of gemcitabine, *nab*-paclitaxel, dexamethasone, carfilzomib, bortezomib, lenalidomide, pomalidomide, azacitidine, or PI3Kδ inhibitor (Phase 1b and Phase 2 only, as appropriate to treatment cohort).
17. Ongoing radiation therapy and/or radiation therapy administered within 15 days of enrollment; subject must not require corticosteroids and must have recovered from all ongoing radiotherapy-related toxicities.
    - Subjects who have received radiation to the spine, pelvis, ribs, or femur should be discussed with the sponsor, as extensive radiation to a marrow-forming region may compromise a subject's ability to tolerate myelosuppressive chemotherapy.
18. Subjects who, in the opinion of the investigator, are unable or unlikely to comply with the administrative schedule and study evaluations, including the ability to swallow an oral agent.
19. Any serious medical condition that, in the opinion of the investigator, would pose a significant risk to the subject or interfere with the interpretation of the study data.
20. Current clinically active and uncontrolled infection of any etiology.
21. Subjects with baseline serum (1,3)-β-D-glucan values > 60 pg/mL (Cohort H only).

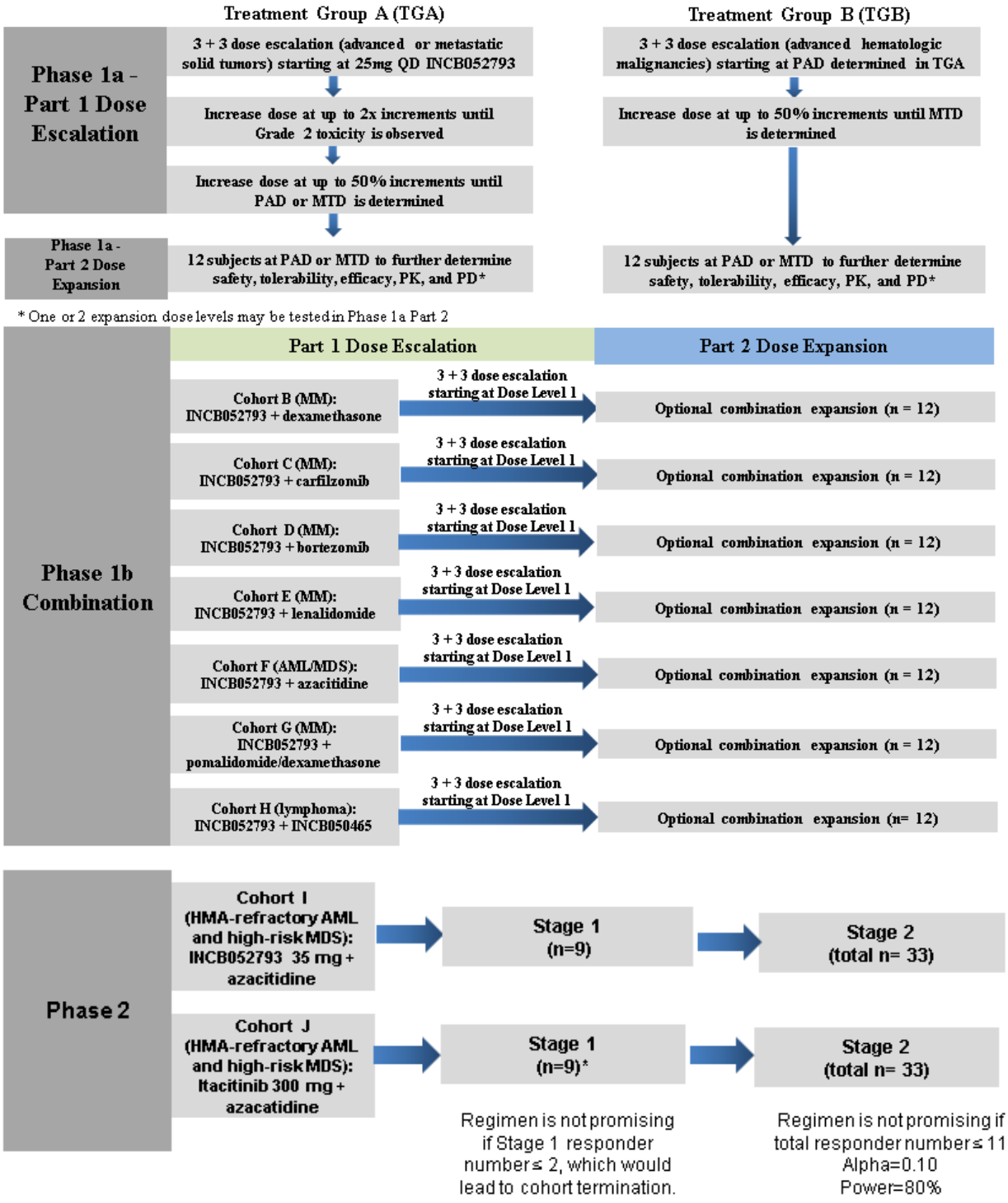
4. INVESTIGATIONAL PLAN

The investigational agent in this study is INCB052793, hereafter referred to as study drug. All study subjects will receive the study drug in an open-label manner as an oral, self-administered agent.

4.1. Overall Study Design

The study will be conducted in 2 phases (Phase 1a/1b and Phase 2). Phase 1a will be conducted with INCB052793 monotherapy dose escalation (Part 1) and dose expansion (Part 2). Phase 1b will comprise treatment cohorts in which INCB052793 will be administered in combination with gemcitabine and *nab*-paclitaxel in select solid tumors (Cohort A); dexamethasone, carfilzomib, bortezomib, lenalidomide, and pomalidomide/dexamethasone in subjects with MM (Cohorts B, C, D, E, and G, respectively); azacitidine in subjects with AML or MDS (Cohort F), and INCB050465 in subjects with lymphoma (Cohort H), each including both a dose escalation (Part 1) and an optional dose expansion (Part 2). Phase 2 will include 2 treatment cohorts in which subjects with AML and high-risk MDS who failed prior therapy with HMA will receive azacitidine in combination with INCB052793 (Cohort I) or in combination with itacitinib (Cohort J). Those cohorts will use a Simon 2-stage design to evaluate the efficacy of the combination regimens. The approximate numbers of subjects for Stage 1 and Stage 2 are described in Section 9. If an insufficient number of responders are observed in the cohort at Stage 1, further enrollment in the cohort will be terminated; see Figure 2).

Figure 2: Study Design



* The first 3-6 subjects enrolled in Cohort J will be monitored for occurrence of DLTs before enrollment of more subjects. If this dose exceeds the MTD, the subjects enrolled at this dose level will not be analyzed for efficacy and will be replaced with new subjects enrolled at 200 mg QD and will be monitored as above. If this dose is not tolerable, the cohort will be discontinued.

4.1.1. Phase 1a Monotherapy

Phase 1a will include Part 1 dose escalation starting with 25 mg QD to determine the MTD and/or PAD of single-agent INCB052793 in 2 treatment groups (TGA and TGB). This dose will be chosen for further evaluation. Part 2 dose expansion will evaluate the chosen dose as monotherapy.

4.1.1.1. Phase 1a Part 1 Dose Escalation

The dose escalation will start with TGA (advanced or metastatic solid tumors) at 25 mg QD and consist of a 21-day cycle, with Cycle 1 Day 1 as the first day of treatment. Open-label dose escalation will consist of an initial cohort using a 3 + 3 design with dose doubling until either Grade 2 or greater toxicities or unbound AUC at steady state exceeds the value (25.3 μM·h) corresponding to the NOAEL in the most sensitive species evaluated in GLP toxicology studies (rat at 15 mg/kg). Each dose level will be observed for a period of 21 days before enrolling the next cohort and administering the next dose level. Treatment Group B (advanced hematologic malignancies) will follow the same 3 + 3 dose-escalation design, beginning enrollment at the PAD when it is determined. If warranted, lower dose levels may be explored during the dose escalation to further evaluate the safety, PK, [redacted] profile of INCB052793.

Subjects who receive at least 17 of 21 days (or ≥ 80%) of fasted study drug at the level assigned to that cohort, or who experience a DLT, will be considered evaluable for determining tolerability of dose (see Section 4.2). Subjects enrolling but not meeting these criteria may be replaced in order to fill the cohort.

The starting dose of INCB052793 (25 mg QD in TGA; PAD in TGB) will be escalated if 0 of the first 3 evaluable subjects enrolled experience a DLT. Increases to study drug will be up to 100% (ie, 25 mg, 50 mg, 100 mg, and 150 mg) if there are no reported Grade 2 or greater toxicities and no subject has an unbound AUC at steady state that exceeds 25.3 μM·h. Otherwise, increases of study drug dose will be limited to no more than 50% in successive cohorts, using QD regimen (ie, 25 mg, 35 mg, 50 mg, 75 mg, 100 mg, and 150 mg). If no DLTs are observed in the initial 3 subjects, the next cohort will begin enrollment. If 1 DLT is observed in the first 3 subjects, 3 additional subjects will be enrolled in the cohort.

4.1.1.2. Phase 1a Part 2 Dose Expansion

The expansion may proceed with a PAD, the MTD, or the highest dose tested if the MTD is not reached:

- TGA (advanced or metastatic solid tumors) and TGB (advanced hematologic malignancies) of approximately 12 subjects each in 1 or 2 expansion dose levels (PAD and/or MTD or highest dose tested if MTD is not reached for each group tested) will be treated with the selected doses of INCB052793 as a single agent to further determine safety, tolerability, efficacy, PK, [redacted] in this population.
- For both TGA and TGB, a study of the effect of food on the PK of INCB052793 will be conducted on this expanded cohort. Results from the food-effect study will dictate whether study drug will be administered to subjects in the fasted or fed state in ongoing subjects in Phase 1a and Phase 1b.

4.1.2. Phase 1b Combination Therapy

Phase 1b will comprise treatment cohorts evaluating INCB052793 when administered in combination with standard therapies for select solid tumors (Cohort A), MM (Cohorts B, C, D, E, and G), AML/MDS (Cohort F), and with the novel PI3Kδ inhibitor INCB050465 in lymphoma (Cohort H). Each treatment cohort will include 2 parts. Part 1 is a 3 + 3 dose escalation that will evaluate increasing doses of INCB052793 in combination with standard-of-care agents or INCB050465 in select solid tumors, MM, AML/MDS, and lymphoma. Part 2 will be an optional expansion to further evaluate the safety and preliminary efficacy of the combination at the selected INCB052973 dose. Timing for the initiation of Phase 1b enrollment will be determined by the sponsor based on the available safety/tolerability and PK/[redacted] data from Phase 1a. The sponsor may elect to open certain Phase 1b treatment cohorts before others or to not open specific cohorts.

Enrollment into Cohorts A, C, D, E, G, and H will not be conducted as per Amendment 7 of the Protocol.

If a subject does not meet eligibility criteria for the next treatment cohort in sequence due to a specific criterion (eg, pre-existing ≥ Grade 2 peripheral neuropathy excluding the subject from Cohort D), the subject will be enrolled into the next open cohort.

4.1.2.1. Phase 1b Part 1 Dose Escalation

The starting dose of INCB052793 in each treatment cohort will be designated as Dose Level 1. Dose Level 1 will be approximately 50% to 100% of a PAD (maximum of 75% of MTD) in Phase 1a (rounded down to the next lowest dose based on available tablet strengths). Dose escalation will proceed using a 3 + 3 design as described in Section 4.2. Each cohort will be observed for a minimum of 1 cycle before the next cohort begins enrollment. Within each cohort, subjects will be considered nonevaluable for safety and replaced if they have received < 75% of the planned doses of study drug or standard therapy during the first cycle of treatment and they have not experienced a DLT. If Dose Level 1 is deemed tolerable, the INCB052793 dose in the respective combination therapy may be escalated to Dose Level 2, which will be ≤ 50% higher than Dose Level 1. Additional dose levels may be enrolled (ie, Dose Level 3, Dose Level 4, etc) until the MTD has been exceeded, with individual dose increases not to exceed ≤ 50%. If Dose Level 1 is deemed to have exceeded the MTD, Dose Level -1 of INCB052793 (defined as 50%-75% of Dose Level 1) may be evaluated.

The initial dose of INCB050465 will be 20 mg QD in Cohort H. This dose level is considered a PAD. However, based on emerging PK, [redacted] safety, and efficacy data, subjects may be enrolled at a different dose (eg, 30 mg or 15 mg) in combination with the recommended dose of INCB052793. The individual dose increases will not to exceed 50%. The MTD of monotherapy for both agents will not be exceeded.

4.1.2.2. Phase 1b Part 2 Dose Expansion

This portion will explore the safety, tolerability, PK, [redacted] and preliminary clinical activity of the regimen identified in the dose-escalation portion through an optional expansion cohort of approximately 12 subjects per cohort, to be treated at the combination doses selected in Part 1.

4.1.3. Phase 2

Phase 2 includes 2 treatment cohorts in which subjects with AML and high-risk MDS who failed prior therapy with HMA will receive azacitidine in combination with INCB052793 35 mg QD (Cohort I) or in combination with itacitinib 300 mg QD (Cohort J). The first 3 to 6 subjects enrolled in Cohort J in Stage 1 will be followed for occurrence of DLTs before enrollment of more subjects. If this dose exceeds the MTD, the subjects enrolled at this dose level will not be analyzed for efficacy and will be replaced with new subjects enrolled at 200 mg QD and followed as above. If 200 mg is not tolerable, further enrollment in the cohort will be terminated.

Enrollment into Cohorts I and J will proceed in sequence (eg. first subject enrolled in Cohort I, next subject enrolled in Cohort J, etc) until both cohorts have been fully enrolled.

A Simon 2-stage design will be used to evaluate the efficacy of the combination regimens in these cohorts. The approximate numbers of subjects for Stage 1 and Stage 2 are specified in Figure 2 and described in more detail in Section 9. If an insufficient number of responders are observed in the cohort at Stage 1, further enrollment in the cohort will be terminated.

4.2. Dose-Limiting Toxicity Rules

For Phase 1a/Part 1 and Phase 1b/Part 1, if no DLTs are observed in the initial 3 subjects, the next cohort will begin enrollment. If 1 DLT is observed in the first 3 subjects, 3 additional subjects will be enrolled in the cohort. If a DLT occurs in one-third or more of the total cohort ($\geq$ 2 of 3 or 6), then the MTD will be deemed to have been exceeded, and the next lower dose level will be deemed to be the MTD. If the dose-escalation increment has been 100%, then an intermediate lower dose level may be explored. Thus, the MTD will be defined as 1 dose level below that at which one-third or more of subjects in a particular cohort experience DLTs. Dose-limiting toxicities occurring during the first 21- or 28-day treatment cycle will guide dose escalation and determination of the MTD; however, subjects who may have not experienced a DLT but who experienced intolerable, lower grade persistent toxicity determined to be due to study drug will be considered in the determination of the study drug dose in the expansion cohorts. Likewise, when an additional agent is added after disease progression or absence of response (eg, dexamethasone may be added to INCB052793/lenalidomide), subjects will be observed for DLTs and persistent toxicities in this setting in same manner as the dose-escalation portion, and the drug will be similarly dose reduced or discontinued as indicated. Only toxicities with a clear alternative explanation (ie, due to disease progression, comorbid condition, concomitant medication) can be deemed a non-DLT for determination of the PAD/MTD.

In Phase 2, subjects will receive azacitidine in combination with INCB052793 35 mg QD (Cohort I) or in combination with itacitinib 300 mg QD (Cohort J). See Section 4.1.3 for more details.

4.2.1. Definition of Dose-Limiting Toxicities

Specific AEs occurring during Cycle 1 of the study, or in the first cycle of treatment in which an additional agent is added to the combination in the setting of prolonged stable disease or progressive disease (Phase 1b Cohorts B, C, D and E only), will be considered to be DLTs if they are not clearly related to the underlying disease or its progression, comorbidity, and

concomitant medication. Dose-limiting toxicities occurring during the first cycle will guide dose escalation and determination of the MTD. Subjects who may have not experienced a DLT but who experienced intolerable, lower grade persistent toxicity determined to be due to study drug or have experienced recurrent dose interruptions and/or reductions will be considered in the determination of the study drug dose in the expansion cohorts. A DLT will be defined as an AE that is new in onset and meets any of the following criteria, using the NCI CTCAE v4.03 toxicity grading scale:

Hematologic Toxicities:

Phase 1a and Phase 1b/Cohorts A through H (except F):

- Grade 3 thrombocytopenia with bleeding requiring transfusion.
- Grade 4 thrombocytopenia.
- Grade 4 neutropenia.
  - Note: For solid tumors only: Grade 3 neutropenia is not considered a DLT; however, it may contribute to defining the MTD if more than two-thirds of subjects in a cohort (eg, 3 of 3 subjects or ≥ 5 of 6 subjects) experience neutropenia lasting ≥ 3 days after interruption of INCB052793.
- Grade 4 anemia.
- Febrile neutropenia (ANC < 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 > 1 hour.

Phase 1b/Cohort F and Phase 2:

- Grade 4 thrombocytopenia or requirement for platelet transfusion persisting for more than 6 weeks after initiation of treatment in subjects whose bone marrow assessment showed less than 5% blasts and no significant dysplasia.
- Grade 4 neutropenia persistent for more than 6 weeks after initiation of treatment in subjects whose bone marrow assessment showed less than 5% blasts and no significant dysplasia.
- Given the high frequency of prevalence of disease-related cytopenias and infectious complications in AML and high-risk MDS population events related to underlying disease, including but not limited to bleeding, infection, and febrile neutropenia, are not considered DLTs unless severity or duration is longer than that expected with standard of care treatment.

Nonhematologic Toxicities:

- Grade 2 peripheral neuropathy with pain (except Phase 1b/Cohort D).
- Any ≥ Grade 3 nonhematologic toxicity EXCEPT:
  - Grade 3 nausea, vomiting, and diarrhea adequately controlled with medical therapy in ≤ 72 hours.
  - Fasting glucose > 250 mg/dL occurring within 3 days after dexamethasone administration (exception not applicable in Phase 2).

  - Total bilirubin ≥ 2.0 × ULN to ≤ 3.0 × ULN that reverses to baseline within 7 days and Grade 3 ALP, AST, or ALT that reverses to baseline within 7 days, except cases meeting the criteria for Hy's Law described below. Grade 3 and 4 ALP elevations in subjects with bone metastasis. **Note:** All Grade 3 bilirubin elevations regardless of duration will be considered a DLT in Phase 2.

- Liver abnormalities meeting the criteria for Hy's Law (ALT or AST > 3 × ULN and total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP) 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) known to be hepatotoxic.

Subjects who experience a Grade 4 nonhematologic DLT should discontinue treatment. Dose-finding decisions will consider all available data, including the safety profile of prior cohorts. The decision for the subsequent cohorts and rationale will be documented in writing. Selected dose cohorts may have additional subjects added in order to further assess safety, PK, [redacted].

Each cohort will be observed for a minimum of either 21 days (Phase 1a and Phase 1b/Cohorts D and H) or 28 days (Phase 1b/Cohorts A, B, C, E, F, and G) before the next cohort begins enrollment. Within each cohort, subjects will be considered nonevaluable for safety and replaced if they have not experienced a DLT and: a) they have not received the specified dose of INCB052793 for at least 17 of 21 doses in Phase 1a and 75% of the planned doses of study drug or standard therapy during the first cycle of treatment in Phase 1b (unless the drug hold was due to a DLT). Additional subjects may be enrolled to ensure there are enough evaluable subjects for safety.

In Phase 2, a Simon 2-stage design will be used for Cohorts I and J. In addition, the first 3 to 6 subjects enrolled in Cohort J in Stage 1 will be followed for occurrence of DLTs before enrollment of more subjects. See Section 4.1.3 for more details.

4.3. Study Endpoints

4.3.1. Primary Endpoints

Phase 1a and 1b:

- Safety and tolerability of INCB052793 monotherapy and in combination with standard therapies in select malignancies as assessed by summary of clinical laboratory assessments, 12-lead ECGs, and AEs.

Phase 2:

- ORR, defined as the proportion of subjects who achieve CR, CR with incomplete hematologic recovery (CRi), partial response (PR), or HI, using the appropriate disease-specific criteria.

4.3.2. Secondary Endpoints

- Response rates in those subjects with measurable disease as determined by investigator assessment of response.

- Safety and tolerability of INCB052793 in combination with azacitidine and of itacitinib in combination with azacitidine in subjects with AML and high-risk MDS who have failed prior therapy with HMA, assessed by summary of clinical laboratory assessments, 12-lead ECGs, and AEs.
- Pharmacokinetics of INCB052793 and itacitinib (Phase 1a, Phase 1b, and Phase 2) will be summarized.
- For Phase 1a Part 2 expansion portion (TGA and TGB), C_{max}, T_{max}, and AUC_{0-t} for Cycle 1 Day 1 and C_{max}, T_{max}, C_{min}, AUC_{0-t}, and $AUC_{0-\tau}$ for Cycle 1 Day 15, or C_{max}, T_{max}, C_{min}, AUC_{0-t}, and $AUC_{0-\tau}$ for Cycle 2 Day 1 in the case of food-effect evaluation.

4.4. 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 are made.

4.5. Number of Subjects

Up to approximately 141 subjects may be enrolled, with 36 subjects in Phase 1a, up to approximately 39 subjects in Phase 1b, and approximately 18 to 66 subjects in Phase 2. The number of subjects in Phase 2 will depend on the observed tolerability and the number of responders.

4.6. Study Termination

The sponsor may terminate the study electively or if required by regulatory decision. If the study is terminated prematurely, the sponsor will notify the investigators, the institutional review boards (IRBs) and/or independent ethics committees (IECs), and regulatory bodies of the decision and the reason for termination of the study.

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB or IEC in writing of the study's completion or early termination, and 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 OF SUBJECTS

5.1. Treatment Groups and Administration of Study Drug

5.1.1. Phase 1a Monotherapy

5.1.1.1. INCB052793

Subjects will self-administer INCB052793 orally with water; according to a QD morning regimen as directed by the investigator (dosing may be switched to BID dosing based on emerging PK [redacted] data). INCB052793 will be taken on an empty stomach by refraining from food consumption for 2 hours before and 1 hour after study drug administration except on days when PK samples are collected (see Section 7.7 for PK dosing instructions), when it will be taken after an overnight fast of at least 8 hours. Subjects will take study drug at the clinic after the hematology sample is drawn on clinic days when a hematology sample is obtained. One cycle will be defined as 21 continuous days of planned study treatment; subjects will receive treatment in continuous cycles.

5.1.2. Phase 1b Combination Therapy

5.1.2.1. INCB052793

Subjects will self-administer INCB052793 orally with water according to a QD morning regimen as directed by the investigator (dosing may be switched to BID dosing based on emerging PK [redacted] data). INCB052793 will be taken on an empty stomach by refraining from food consumption for 2 hours before and 1 hour after study drug administration, except on days when PK samples are taken (see Section 7.7). Subjects will take study drug at the clinic after the hematology sample is drawn on clinic days when a hematology sample is obtained. One cycle will be defined as 21 (Cohorts D and H) or 28 (Cohorts A, B, C, E, F, and G) continuous days of planned study treatment.

5.1.2.2. *nab*-Paclitaxel

nab-Paclitaxel (Abraxane®) 125 mg/m^2 should be administered as a 30-minute IV infusion once weekly for 3 consecutive weeks out of every 4 weeks (on Days 1, 8, and 15 of each 28-day cycle). Although the starting dose of *nab*-paclitaxel in Phase 1b will be 125 mg/m^2; a lower dose of 100 mg/m^2 may be explored if necessary.

5.1.2.3. Gemcitabine

Gemcitabine (Gemzar® or equivalent) 1000 mg/m^2 should be administered as a 30-minute IV infusion once weekly for 3 consecutive weeks out of every 4 weeks (on Days 1, 8, and 15 of each 28-day cycle). The infusion of gemcitabine must begin after completion of the *nab*-paclitaxel infusion. Increased toxicity has been observed if gemcitabine is administered more frequently than once weekly or infusions that last longer than 60 minutes. The starting dose of gemcitabine in Phase 1b will be 1000 mg/m^2; a lower dose of 750 mg/m^2 may be explored if necessary.

5.1.2.4. Dexamethasone

Dexamethasone will be administered as open-label commercial product at a starting dose of 40 mg administered orally weekly on Days 1, 8, 15, and 22 of each 28-day cycle, without regard to food. Dose adjustments for toxicity will be permitted at the discretion of the investigator. After 4 or more cycles of stable disease, or if disease progression occurs after 1 or more cycles of the combination, carfilzomib, bortezomib or lenalidomide (at the discretion of the investigator) may be added to the regimen at a dose level that has been determined as safe and tolerable in the relevant treatment cohort (C, D, or E). If an additional agent is added to the regimen, the subject will subsequently follow the schedule of assessments appropriate to that agent.

5.1.2.5. Carfilzomib

Carfilzomib (Kyprolis 2012) will be administered as an open-label commercial product at a dose of 20 mg/m^2 IV on Days 1 and 2 followed by 27 mg/m^2 IV on Days 8, 9, 15, and 16 of Cycle 1 and for all doses of each 28-day cycle thereafter. After 4 or more cycles of stable disease, or if disease progression occurs after 1 or more cycles of the combination, dexamethasone 40 mg administered orally weekly may be added to the regimen and continued until study withdrawal. The sponsor may implement weekly dexamethasone into combination from Cycle 1, based on emerging data either by an administrative memorandum or a Protocol amendment. After 12 cycles of treatment, subjects will transition to maintenance dosing on Days 1, 2, 15, and 16 of each 28-day cycle. Antiviral prophylaxis should be implemented as needed, per institutional standard. Dose adjustments for toxicity will be permitted at the discretion of the investigator.

[redacted]

5.1.2.6. Bortezomib

Bortezomib (Velcade 2014) will be administered as an open-label commercial product at a starting dose of 1.3 mg/m^2 IV or SC on Days 1, 4, 8, and 11 of each 21-day treatment cycle. After 4 or more cycles of stable disease, or if disease progression occurs after 1 or more cycles of the combination, dexamethasone 40 mg administered orally weekly may be added to the regimen and continued until study withdrawal. The sponsor may implement weekly dexamethasone into combination from Cycle 1, based on emerging data either by an administrative memorandum or a Protocol amendment. After 8 cycles, subjects may transition to a maintenance schedule comprising 1 dose every 2 weeks. Antiviral prophylaxis should be implemented as needed, per institutional standard. Dose adjustments for toxicity will be permitted at the discretion of the investigator.

5.1.2.7. Lenalidomide

Lenalidomide (Revlimid 2015) will be administered as an open-label commercial product at a starting dose of 25 mg administered orally QD on Days 1 to 21 of each 28-day cycle. Lower dose levels of lenalidomide may be explored (eg, 10 mg, 15 mg, 20 mg) based on the safety/tolerability of the combination. After 4 or more cycles of stable disease, or if disease progression occurs after 1 or more cycles of the combination, dexamethasone 40 mg administered orally weekly may be added to the regimen until study withdrawal. The sponsor may implement weekly dexamethasone into combination from Cycle 1, based on emerging data either by an administrative memorandum or a Protocol amendment. Dose adjustments for

toxicity will be permitted at the discretion of the investigator. Antithrombotic prophylaxis should be implemented as needed, per institutional standard. Dose adjustments for toxicity will be permitted at the discretion of the investigator.

5.1.2.8. Azacitidine

Azacitidine (Vidaza 2014) will be administered as an open-label commercial product at a dose of 75 mg/m^2 SC for 5 days, followed by 2 days of no treatment, then 75 mg/m^2 for 2 days of each 28-day treatment cycle. Dose adjustments for toxicity will be permitted at the discretion of the investigator. Intravenous administration is allowed if SC administration is not tolerated.

5.1.2.9. Pomalidomide

Pomalidomide will be administered as an open-label commercial product at a dose of 4 mg administered orally QD on Days 1 through 21 of each 28-day cycle. Lower dose levels of pomalidomide may be explored (eg, 3 mg, 2 mg, 1 mg) based on the safety/tolerability of the combination. Dose adjustments for toxicity will be permitted at the discretion of the investigator. Dexamethasone will be coadministered at 40 mg orally weekly on Days 1, 8, 15, and 22 of each 28-day cycle.

5.1.2.10. INCB050465

The initial starting dose of INCB050465 will be 20 mg QD. Subjects may be enrolled at a different dose (eg, 30 mg or 15 mg) based on emerging data. Subjects will self-administer INCB050465 using an oral daily QD regimen, as instructed by the investigator. INCB050465 should be administered in the clinic on days when PK sampling is performed as per Table 19. INCB050465 should be taken on an empty stomach if possible, and subjects should refrain from food consumption during the period 2 hours before and 1 hour after INCB050465 administration.

5.1.3. Phase 2

5.1.3.1. INCB052793

The dose of INCB052793 in Phase 2 will be 35 mg QD. Subjects will self-administer INCB052793 orally with water according to a QD morning regimen as directed by the investigator (dosing may be switched to BID dosing based on emerging PK [redacted] data). INCB052793 will be taken on an empty stomach by refraining from food consumption for 2 hours before and 1 hour after study drug administration, except on days when PK samples are taken (see Section 7.7). Subjects will take study drug at the clinic after the hematology sample is drawn on clinic days when a hematology sample is obtained. One cycle will be defined 28 days of continuous days of planned study treatment.

5.1.3.2. Itacitinib

The starting dose of itacitinib in Phase 2 will be 300 mg QD. Subjects may be enrolled at a different dose (eg, 200 mg QD) based on emerging data. Subjects will self-administer itacitinib orally with water according to a QD morning regimen as directed by the investigator. Itacitinib may be taken without regard to food except on days when PK samples are drawn (see Section 7.7). Subjects will take study drug at the clinic after the hematology sample is drawn on

clinic days when a hematology sample is obtained. One cycle will be defined as 28 days of continuous days of planned study treatment.

5.1.3.3. Azacitidine

Azacitidine will be administered as described in Section 5.1.2.8.

5.2. Treatment Compliance

Subjects should be counseled by the investigator to maintain strict adherence to the study regimen as prescribed and to keep a record of any missed doses or doses taken nonfasted. Subjects will be instructed to bring all unopened, empty, and opened/partially used bottles of study drug to each study visit, at which time compliance will be assessed.

5.3. Randomization and Blinding

In Phase 2, enrollment into Cohorts I and J will proceed in sequence (eg, first subject enrolled in Cohort I, next subject enrolled in Cohort J, etc) until both cohorts have been fully enrolled.

5.4. Duration of Treatment and Subject Participation

Subjects will be treated in continuous 21-day cycles (Phase 1a and Phase 1b/Cohorts D and H) or 28-day cycles (Phase 1b/Cohorts A, B, C, E, F, and G, and Phase 2/Cohorts I and J) until they meet withdrawal criteria as described in Section 5.7.1. If the subject discontinues all study treatment, the treatment portion will end, and the subject will enter the follow-up portion (see Section 6.4). Study participation is expected to average about 6 months.

5.5. Rationale for Dose Modification

Selections and modifications to study drug doses are planned for dose-escalation cohorts. Also, dose interruptions and modifications 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.

In Phase 1a, 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 (See Section 5.6.1).

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

A DLT will be defined as the occurrence of any of the toxicities occurring during the first cycle of treatment, or in the first cycle of treatment in which an additional agent is added to the combination in the setting of prolonged stable disease or progressive disease. The DLTs include AEs that are new in onset and are of the specified grades (see Section 4.2.1), regardless of investigator assessment of causality to the investigational product. Only toxicities with a clear alternative explanation (eg, due to disease progression, comorbidities, and concomitant medications) can be deemed a non-DLT. Subjects who may have not experienced a DLT but who experienced intolerable, lower grade persistent toxicity determined to be due to study drug or have experienced recurrent dose interruptions and/or reductions will be considered in the determination of the study drug dose in the expansion cohorts.

Individual subject dose reductions may be made based on events observed at any time during treatment with INCB052793 and itacitinib; however, for the purposes of dose escalation/ de-escalation, expanding a dose cohort, and determining the MTD of INCB052793 and itacitinib, decisions will be made based on events that are observed from the first day of INCB052793 and itacitinib administration through and including the final day of Cycle 1.

All DLTs will be assessed by the investigator using the current CTCAE v4.03 criteria (NCI 2010).

5.5.2. Follow-Up of Dose-Limiting Toxicities

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

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

In all cases investigators are free to use any measures or concomitant medications, following discussion with the sponsor (whenever possible), necessary to optimally treat the subject.

5.6. Dose Adjustment of Study Drug

5.6.1. Planned Dose Adjustments

Intrasubject dose escalation will be allowed in Phase 1a or Phase 1b, provided that the following criteria are met:

- The Protocol eligibility criteria are met at the time of escalation.
- The subject has received 2 cycles of study drug and standard-of-care agent (as applicable) and has not experienced toxicity ≥ Grade 2 that is NOT from the underlying malignancy.
- The next dose level has been determined to be safe based on DLT rules.
- The subject is willing to repeat all assessments as per Cycle 1, including the PK sampling and ECG schedule as in Cycle 1.
- 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.
- The intrasubject dose escalation has been approved by the sponsor.

In Phase 2, the first 3 to 6 subjects enrolled in Cohort J will be monitored for occurrence of DLTs before enrollment of more subjects. If this dose exceeds the MTD, the subjects enrolled at this dose level will not be analyzed for efficacy and will be replaced with new subjects enrolled at 200 mg QD and will be monitored as above. If this dose is not tolerable, the cohort will be discontinued.

5.6.2. Criteria and Procedures for Interruption

Treatment with INCB052793, INCB050465, and itacitinib may be delayed up to 2 weeks (14 days) to allow for resolution of toxicity or performance of a medical procedure (eg, radiation therapy to an individual lesion with otherwise disease stability). 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's medical monitor to discuss the case of any subject whose treatment has been delayed for more than 14 days before restarting treatment with INCB052793, INCB050465, and/or itacitinib (see Table 1).

5.6.2.1. INCB052793, INCB050465, and Itacitinib Dose Interruption and Restart Guidelines

Because subjects may enter the study with extensive pretreatment, these dose reduction and interruption rules are provided as guidelines (see Table 1). 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. Subjects receiving dose reductions (but not meeting DLT criteria) during the first cycle for that cohort will not be considered evaluable for the purposes of determining the MTD and will be replaced.

Table 1: Guidelines for Interruption and Restart of Study Drugs INCB052793, INCB050465, and Itacitinib

Toxicity/CTCAE Grade	Action Taken
Chemistry: • Total bilirubin > 3.0 × ULN • AST and/or ALT > 3.0 × ULN • ALP ≥ 2.5 × ULN Note: In subjects with bone metastasis-related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.	**Step 1:** Interrupt study drug(s) up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except by approval of the medical monitor. **Step 2:** Restart study drug(s) at next lower dose (or at 25% reduction if in expansion cohort, rounded down to the nearest pill strength); monitor as clinically indicated.[a]
Chemistry: • ALT > 3.0 × ULN, ALP < 2 × ULN, and bilirubin ≥ 2.0 × ULN (Hy's Law)	Discontinue treatment.
Hematology: **Phase 1a/TGA and Phase 1b/Cohort A:** • ANC < 1.0 × 10^9/L • Platelet count 50 to < 75 × 10^9/L **Phase 1a/TGB and Phase 1b/Cohorts B through H (except F):** • ANC < 0.5 × 10^9/L • Platelet count 25 to < 50 × 10^9/L	**Phase 1a/TGA and Phase 1b/Cohort A:** **Step 1:** Hold until resolved to ≥ 1.0 × 10^9/L ANC or ≥ 75 × 10^9/L platelets. **Step 2:** Restart study drug at same dose and monitor as clinically indicated. **Phase 1a/TGB and Phase 1b/Cohorts B through H (except F):** **Step 1:** Hold until resolved to ≥ 0.5 × 10^9/L ANC or ≥ 50 × 10^9/L platelets. **Step 2:** Restart study drug(s) at same dose and monitor as clinically indicated.

Table 1: Guidelines for Interruption and Restart of Study Drugs INCB052793, INCB050465, and Itacitinib (Continued)

Toxicity/CTCAE Grade	Action Taken
Phase 1a/TGA and Phase 1b/Cohort A: • Grade 4 ANC (< 0.5×10^9/L) OR ≥ Grade 3 ANC with an oral temperature of at least 38.5°C OR with ≥ Grade 3 infection • Platelet count < 50×10^9/L	**Phase 1a/TGA and Phase 1b/Cohort A:** **Step 1:** Hold until resolved to ≥ 1.0×10^9/L ANC or 75×10^9/L platelets. **Step 2:** Restart study drug at next lower dose (or 25% reduction if in expansion cohort, rounded down to the nearest tablet strength); monitor as clinically indicated.[a]
Phase 1a/TGB and Phase 1b/Cohorts B through H (except F): • Grade 4 ANC (< 0.5×10^9/L) and 1 or more of the following: – Oral temperature of at least 38.5°C – ≥ Grade 3 infection • Platelet count < 25×10^9/L	**Phase 1a/TGB and Phase 1b/Cohorts B through H (except F):** **Step 1:** Hold until resolved to ≥ 0.5×10^9/L ANC and afebrile or ≥ 50×10^9/L platelets. **Step 2:** Restart study drug(s) at next lower dose (or 25% reduction if in expansion cohort, rounded down to the nearest tablet strength); monitor as clinically indicated.[a]
Phase 1b/Cohort F and Phase 2/Cohorts I and J: • ≥ 50% decrease from baseline platelet count (**Subjects with baseline platelet count < 75×10^9/L only**) • ≥ 50% decrease from baseline ANC (**Subjects in Phase 1b/Cohort F and Phase 2/ Cohorts I and J with baseline ANC < 1.0×10^9/L only**)	**Step 1:** Evaluate underlying disease based on peripheral blood and bone marrow assessment as needed **Step 2:** Consider dose interruption if cytopenias are NOT due to underlying disease or treatment with azacitidine. **Step 3:** Restart study drug at next lower dose (or 25% reduction if in expansion cohort, rounded down to the nearest tablet strength); monitor as clinically indicated.[a]
Other toxicities:	
Any Grade 1 or Grade 2 toxicity	Continue study drug treatment and treat the toxicity; monitor as clinically indicated.
Any Grade 3 toxicity, if clinically significant and not manageable by supportive care	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until toxicity resolves to ≤ Grade 1. **Step 2:** Restart study drug at next lower dose (or 25% reduction if in expansion cohort, rounded down to the nearest pill strength); monitor as clinically indicated.[a]
Any recurrent Grade 3 toxicity after 2 dose reductions	Discontinue study drug treatment and follow-up per Protocol.
Any other Grade 4 toxicity	Discontinue study drug treatment.

[a] Only 2 dose reductions are permitted.

5.6.2.2. Standard-of-Care Dose Interruptions

Dose interruptions and adjustments for standard-of-care agents in Phase 1b and Phase 2 of the study will be at the discretion of the investigator, in accordance with the package insert and applicable treatment guidelines (eg, NCCN Guidelines). In the event that > 2 dose reductions of any standard-of-care agent are required, the subject should be withdrawn from the study as per Section 5.6.3.

5.6.3. Criteria for Permanent Discontinuation of Study Drug or Standard-of-Care Agents

The occurrence of unacceptable toxicity not from the underlying malignancy will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as:

- Occurrence of an AE that is not clearly unrelated 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.
- Toxicity requiring > 2 dose reductions of INCB052793, itacitinib, or standard-of-care therapy. Subjects enrolled in Phase 1b and Phase 2 who have required > 2 reductions of the standard-of-care agent may remain on INCB052793 monotherapy with sponsor approval.
- Persistent toxicity requiring a delay of therapy for > 2 weeks (14 days).
- Confirmed prolongation of QTcF by > 60 milliseconds or QTcF > 500 milliseconds confirmed by repeat ECG from baseline.

5.7. Withdrawal of Subjects From the Study Treatment

After discontinuation of study treatment, all subjects will remain in the follow-up phase of the study for the collection of safety, subsequent anticancer therapies, and survival, as detailed in Section 6.4. Additionally, subjects who discontinue study treatment without disease progression will continue to have disease assessments until disease progression, until the subject begins a new anticancer treatment, or death (see Section 6.4).

5.7.1. Withdrawal Criteria

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

- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The subject is unwilling to continue receiving study treatment.
- The subject becomes pregnant.
- Consent is withdrawn.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB or IEC.
- Unacceptable toxicity has occurred (see Section 5.6.3).
- 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. Subjects in Phase 1b/Cohort B may remain on study if a proteasome inhibitor or IMiD (as per Section 5.1.2.4) is added to the regimen. Subjects in Cohorts C, D, and E may remain on study after disease progression if dexamethasone is added to the regimen (as per Sections 5.1.2.5, 5.1.2.6, and 5.1.2.7).

A subject **may** be withdrawn from the study:

- If during the course of the study, a subject is found not to have met eligibility criteria. The sponsor's medical monitor, in collaboration with the investigator, will determine if the subject should be withdrawn from the study. See Section 11.3.
- If a subject is noncompliant in the opinion of the investigator. The sponsor should be consulted for instructions on handling the subject.

5.7.2. Withdrawal Procedures

The decision to discontinue study treatment (ie, INCB052793/standard-of-care agent) will not constitute study withdrawal or study completion (see Section 5.7). In the event that the decision is made to discontinue study treatment, the treatment phase will be considered complete and the follow-up phase will begin (see Section 6.4).

Upon discontinuation of study treatment, the end-of-treatment (EOT) visit should be completed as outlined in the schedules of assessments (Table 2, Table 4, Table 6, Table 8, Table 10, Table 12, Table 14, Table 16, Table 18, Table 20, and Table 22). The date of the last dose of study drug will be recorded in the case report form (CRF), and the reason for subject withdrawal will be recorded.

If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (ie, safety, disease assessments, subsequent anticancer treatments and survival), 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 phase of the study for collection of subsequent safety, disease assessments, anticancer treatments and survival. The date the subject was withdrawn from the study and the specific reason for withdrawal will be recorded in the CRF.

Once the decision is made to permanently discontinue the study treatment, the following steps should be followed:

- The study monitor or sponsor must be notified.
- The reasons for withdrawal and the date of last dose of study drug must be documented in the subject's medical record and CRF.
- The EOT visit should be performed.
- Subjects must be followed for safety through the time of the follow-up visit or until study drug-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

Reasonable efforts should be made to have the subject return for a safety follow-up, disease status follow-up, and survival follow-up visits. These visits are described in Section 6.4.

5.8. Concomitant Medications and Measures

All concomitant medications and treatments must be recorded in the CRF. Any prior medication received up to 30 days before enrollment (Cycle 1 Day 1) will be recorded in the CRF as well as any concomitant treatments/procedures that are required to manage a subject's medical condition during the study.

5.8.1. Growth Factor Support

The use of growth factors to treat emerging neutropenia should be based on American Society of Clinical Oncology guidelines for the use of WBC growth factors (Smith et al 2006) and the investigator's clinical judgment. The sponsor recognizes that JAK inhibition may reduce the effectiveness of growth factor support and recommends that appropriate measures are taken relative to withholding study drug in the setting of treatment-emergent neutropenia requiring GCSF.

5.9. Restricted Medications and Measures

- Use of systemic corticosteroid doses > 10 mg/day prednisone (or equivalent) is not permitted from the screening visit through the EOT visit except for transient use of < 3 days. For subjects enrolled in Phase 1b/Cohort B, C, D, or E who are receiving therapeutic doses of dexamethasone (ie, 40 mg weekly), no additional corticosteroids should be administered.
- Use of moderate inducers or inhibitors of CYP3A4 (see Appendix C) should be used with caution, and investigators should seek other options where possible.
- P-glycoprotein substrates of clinical relevance should be used with caution.
- **Phase 1b/Cohort E and G (lenalidomide and pomalidomide) only:** Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution.

5.10. Prohibited Medications and Measures

- Any concomitant use of a JAK inhibitor.
- Phase 1b/Cohort H only: any concomitant use of a PI3K inhibitor.
- Use of potent inducers and inhibitors of CYP3A4 (see Appendix C).

6. STUDY ASSESSMENTS

Study and laboratory assessments will be performed as indicated in Table 2 and Table 3 (Phase 1a), Table 4 through Table 19 (Phase 1b), and Table 20 through Table 23 (Phase 2). The sponsor may request to have scans sent to a centralized reader. [redacted] For instructions on all assessments, see Section 7.

Table 2: Schedule of Assessments for Phase 1a Monotherapy (Dose Escalation and Expansion)

Procedure	Protocol Section	Screening Phase	Treatment Phase (21-Day Cycles)				EOT	Follow-Up Phase		
			Cycle 1[a]			Subsequent Cycles		Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up
		Day -28 to -1	Day 1	Day 8 ± 3 Days	Day 15 ± 3 Days	Day 1 ± 3 Days		30-35 Days After EOT	Every 8 Weeks (± 7 Days) After EOT	Every 12 Weeks (± 7 Days)
Informed consent	7.1	X								
Review inclusion/ exclusion criteria	3	X								
Demography and medical history	7.3.1	X								
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X		
Physical examination/ body weight[b]	7.4.2 7.4.3	X	X	X	X	X	X	X		
Vital signs	7.4.4	X	X	X	X	X	X	X		
12-lead ECG[c]	7.4.5	X	X			X	X			
Timed ECG[c]	7.4.5.1		X		X					
Laboratory tests	7.4.6	X	X	X	X	X	X	X		
ECOG status	7.6	X	X			X	X			
Review of AEs[d]	7.4.1	X	X	X	X	X	X	X		
INCB052793 administer in clinic[e]	7.7.1.1 7.9.1		X	X	X	X				
Assess compliance	7.9.14		X	X	X	X	X			
Distribute reminder cards	7.9.15	X	X	X	X	X	X			
Poststudy disease status	6.4.2								X	
Survival follow-up	6.4.3									X
DISEASE ASSESSMENTS										
AML, MDS, MDS/MPN, MF, and MM response assessment [f]	7.5, 7.4.6.8	X	X			X	X			

Table 2: Schedule of Assessments for Phase 1a Monotherapy (Continued)

Procedure	Protocol Section	Screening Phase	Treatment Phase (21-Day Cycles)				EOT	Follow-Up Phase		
			Cycle 1[a]			Subsequent Cycles		Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up
		Day -28 to -1	Day 1	Day 8 ± 3 Days	Day 15 ± 3 Days	Day 1 ± 3 Days		30-35 Days After EOT	Every 8 Weeks (± 7 Days) After EOT	Every 12 Weeks (± 7 Days)
Immunophenotyping[g]	7.5.5	X				X[g]				
Solid tumors/lymphoma (CT/MRI/FDG-PET)[h]	7.5.1, 7.5.3	X				X	X		X	
Skeletal survey (MM only)[i]	7.5.6	X	X (investigator discretion)							
Bone marrow aspirate and biopsy (hematologic malignancies only)[j]	7.5.4	X				X				
TUMOR TISSUE BIOPSY/ARCHIVAL TISSUE COLLECTION										
Tumor tissue biopsy[k]	7.8.4	X	X							
Buccal swab	7.8.5	X								

CT = computed tomography; FDG-PET = positron emission tomography using [^{18}F] fluorodeoxyglucose; FISH = fluorescence *in situ* hybridization; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] Subjects who escalate their doses will have assessments done as per Cycle 1, including laboratory assessments.

[b] Comprehensive physical examination at screening; targeted physical examination thereafter. Body weight will be taken at each visit. Height is measured at screening only.

[c] Electrocardiograms will be performed at screening, Day 1 of each cycle, and EOT; timed triplicate ECGs will be performed predose and 1 and 2 hours postdose on Cycle 1 Day 1 and Cycle 1 Day 15. The ECGs should be conducted before, but within, 15 minutes of the PK blood draw at the corresponding timepoint.

[d] Subjects must be followed for AEs for 30 days (+ 5 days) after the EOT visit (or after the last dose of study drug if the EOT visit was not performed.)

[e] Study drug will be administered in a fasted state of 2 hours predose and 1 hour postdose with the following exception: on days with PK [redacted] sampling, subjects will fast 8 hours before and 1 hour after study drug administration. Study drug should be administered in the clinic on days where there are PK [redacted] collections as outlined in Sections 7.7 and 7.8. Otherwise, the study drug will be self-administered by the subject.

[f] For subjects with MM, response assessments should be performed as per Section 7.4.6.8 at screening, on Day 1 of each cycle (± 7 days) for the first 12 months of study participation followed by every 12 weeks (every 4 cycles), and EOT. For subjects with AML/MDS/MPN, response assessments should be performed on Day 1 of each cycle and at EOT. In subjects who discontinue study drug without confirmed disease progression, a response assessment should be performed at the time of treatment discontinuation (ie, date of discontinuation ± 4-week window). For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status until (1) start of new anticancer therapy, (2) documented disease progression, (3) death, or (4) the end of study, whichever occurs first. See Section 7.5.

[g] For subjects with lymphomas and AML/MDS, immunophenotyping should be performed at screening, Cycle 2 Day 1, and to confirm a CR.

[h] Computed tomography, MRI, FDG-PET, and/or PET/CT (appropriate to disease type) will be conducted every 6 weeks (every 2 cycles) for the first 12 months of study participation, followed by every 12 weeks (every 4 cycles) until the subject enters into the disease status follow-up phase. Treatment cycles may be delayed; therefore, tumor assessments may be delayed as well to synchronize with treatment cycles regardless if treatment is delayed due to safety (± 10-day window). For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status, including, if applicable, radiographic disease imaging until 1) start of new anticancer therapy, 2) documented disease progression, 3) death, or 4) the end of study, whichever comes first.

[i] Skeletal survey should be conducted at screening and subsequently at the discretion of the investigator.

[j] Subjects with AML, MDS, and MPN should have a bone marrow aspirate at screening and approximately 3, 6, and 12 months after Day 1 and then every 12 months on the nearest Cycle Day 1 (± 7 days) after the first dose of treatment and as clinically indicated. For subjects with lymphoma (with exceptions noted in Section 7.5.4) and MM, a bone marrow examination should be conducted at screening and only if confirming a CR unless otherwise clinically indicated. Fluorescence *in situ* hybridization and cytogenetic testing should be performed, when feasible, as per institutional standard. Bone marrow biopsy should be obtained if needed for disease evaluation (eg, if there are no spicules in the aspirate or in case aspirate cannot be obtained).

[k] Fresh bone marrow aspirate sample is required at baseline for subjects in TGB only. An optional fresh bone marrow aspirate may be obtained at any time during the study, if a bone marrow examination is otherwise performed to assess disease status. Lymphoma subjects in whom a baseline bone marrow biopsy/aspirate is not required as per Section 7.5.4 are exempt from this requirement.

Table 3: Laboratory Assessments for Phase 1a Monotherapy (Dose Escalation and Expansion)

Local Laboratory Tests	Protocol Section	Screening Phase	Treatment Phase (21-Day Cycles)						Safety Follow-Up
			Cycle 1			Cycle 2	Subsequent Cycles (± 3 Days)	EOT	
		Day -28 to -1	Day 1	Day 8 ± 3 Days	Day 15 ± 3 Days	Day 1	Day 1		30-35 Days After EOT
Serum chemistry	7.4.6.1	X	X	X	X	X	X	X	X
Hematology[a]	7.4.6.3	X	X	X	X	X	X	X	X
Coagulation panel[b]	7.4.6.4	X				X	X	X	
Urinalysis[b]	7.4.6.5	X				X	X	X	
Hepatitis serology	7.4.6.7	X							
Central Laboratory Samples									
Expanded serum chemistry	7.4.6.2	X	X	X	X	X	X	X	X
Serum pregnancy[c]	7.4.6.6	X						X	
PK plasma trough (predose)[d]	7.7.1.1		X	X[d]	X	X[d]			
PK TIMED[e]	7.7.1.1		X		X	X[e]			
[redacted]									
Urine sample collection (6-hour)[j]	7.7.2				X				

[a] Study drug should be held on clinic visit days until after the hematology sample is obtained.

[b] Urinalysis and coagulation panel are required at screening, Cycle 2 Day 1, Cycle 4 Day 1, and every third cycle thereafter (Cycles 7, 10, etc); and at EOT.

[c] For women of childbearing potential: local urine pregnancy tests can be done throughout the course of the study at the investigator's discretion.

[d] Cycle 1 Day 1, Cycle 1 Day 15, and Cycle 2 Day 1 (food-effect only) require trough (predose) and timed PK (see footnote e). Day 8 collection is trough (predose) only. No timed sampling required at this visit. Collect trough before morning dose of study drug. Study drug administration will occur in the clinic. Subjects should refrain from eating 8 hours before arriving at the clinic and 1 hour after study drug administration. Cycle 2 Day 1 PK samples will only be collected from subjects in the Phase 1a Part 2 expansion food-effect cohort (See Section 7.7.1.2).

[e] Timed PK: Collect samples predose and 0.5, 1, 2, 4, and 6 hours postdose. Study drug administration will occur in the clinic. Subjects should refrain from eating 8 hours before arriving at the clinic and 1 hour after study drug administration. Cycle 2 Day 1 PK samples will only be collected from subjects in the Phase 1a Part 2 expansion food-effect cohort (see Section 7.7.1.2).

[redacted]

[j] Total urine will be collected over a 6-hour interval after study drug administration for Phase 1a only (see Section 7.7.2).

Table 4: Schedule of Assessments for Phase 1b/Cohort A Combination Therapy (Gemcitabine and *nab*-Paclitaxel)

Procedure	Protocol Section	Screening Phase	Treatment Phase (28-Day Cycles)						EOT	Follow-Up Phase		
			Cycle 1				Subsequent Cycles (± 3 Days)			Safety Follow-Up	Disease Follow-Up	Survival Follow-Up
		Day -28 to -1	Day 1	Day 8 ± 3 Days	Day 15 ± 3 Days	Day 22 ± 3 Days	Day 1	Days 8 and 15		30-35 Days After EOT	Every 8 Weeks	Every 12 Weeks
Informed consent	7.1	X										
Review inclusion/exclusion criteria	3	X										
Demography and medical history	7.3.1	X										
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	X	X		
Physical examination/body weight[a]	7.4.2, 7.4.3	X	X	X	X	X	X	X	X	X		
Vital signs	7.4.4	X	X	X	X	X	X	X	X	X		
12-lead ECG	7.4.5	X	X[b]		X[b]		X		X			
Laboratory tests	7.4.6	X	X	X	X	X	X	X	X	X		
ECOG status	7.6	X	X	X	X		X		X	X		
CT or MRI	7.5.1	X					X[c]					
Review AEs	7.4.1	X	X	X	X	X	X	X	X	X		
INCB052793 dispensing	7.9.4		X				X					
INCB052793 dose at site[d]	7.9.1		X	X	X							
Administration of *nab*-paclitaxel	7.9.5		X	X	X		X	X				
Administration of gemcitabine	7.9.6		X	X	X		X	X				
Assess compliance	7.9.14		X	X	X	X	X	X	X			
Distribute reminder cards	7.9.15	X	X	X	X	X	X	X	X			
Poststudy disease status	6.4.2										X	
Survival follow-up	6.4.3											X

[a] Comprehensive physical examination at screening; targeted physical examination thereafter. Body weight will be taken at each visit. Height will be measured at screening only.
[b] Electrocardiograms will be performed at screening, Day 1 of each cycle, and EOT; triplicate ECGs will be performed predose and 1 and 2 hours postdose on both Cycle 1 Day 1 and Day 15.
[c] A CT (chest, abdomen, and pelvis) or MRI will be conducted every 8 weeks. Treatment cycles may be delayed; therefore, tumor assessments may be delayed as well to synchronize with treatment cycles. Visit window is ± 10 days.
[d] Study drug will be administered in a fasted state of 2 hours predose and 1 hour postdose with the following exception: on days with PK [redacted] sampling, subjects will fast 8 hours before and 1 hour after study drug administration.

Table 5: Laboratory Assessments for Phase 1b/Cohort A Combination Therapy (Gemcitabine and *nab*-Paclitaxel)

Local Laboratory Tests	Protocol Section	Screening Phase	Treatment Phase (28-Day Cycles)						EOT	Safety Follow-Up
			Cycle 1				Subsequent Cycles (± 3 Days)			
		Day -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 1	Days 8 and 15		30-35 Days After EOT
Serum chemistry	7.4.6.1	X	X	X	X	X	X	X	X	X
Hematology[a]	7.4.6.3	X	X	X	X	X	X	X	X	X
Coagulation panel[b]	7.4.6.4	X					X		X	
Urinalysis[b]	7.4.6.5	X					X		X	
Hepatitis serology	7.4.6.7	X								
Central Laboratory Samples										
Expanded serum chemistry	7.4.6.2	X	X	X	X	X	X	X	X	X
Serum pregnancy[c]	7.4.6.6	X					X		X	
PK plasma trough (predose)[d]	7.7.1		X	X	X					
PK plasma TIMED[e]	7.7.1		X		X					
[redacted]										

[a] Study drug, gemcitabine, and *nab*-paclitaxel should be held on clinic visit days until after the hematology sample is obtained.
[b] Urinalysis and coagulation panel are required at screening; Cycle 2 Day 1, Cycle 4 Day 1, and every third cycle thereafter (Cycles 7, 10, etc); and at EOT.
[c] For women of childbearing potential, serum pregnancy testing should be performed at screening, Day 1 of each cycle (beginning with Cycle 2), and EOT. Local urine pregnancy tests can be done throughout the course of the study at the investigator's discretion.
[d] Predose collection of PK trough on Cycle 1 Day 1, 8, and 15.
[e] Collect PK timed samples at 0.5, 1, 2, 3, and 5 hours after the start of *nab*-paclitaxel and gemcitabine infusion. See Section 7.7.1.3 for specific instructions on timings after *nab*-paclitaxel and gemcitabine administration.

[redacted]

Table 6: Schedule of Assessments for Phase 1b/Cohort B Combination Therapy (Dexamethasone)

Procedure	Protocol Section	Screening Phase	Treatment Phase (28-Day Cycles)						EOT	Follow-Up Phase		
			Cycle 1				Subsequent Cycles (± 3 Days)			Safety Follow-Up	Disease Follow-Up	Survival Follow-Up
		Day -28 to -1	Day 1	Day 8 ± 3 Days	Day 15 ± 3 Days	Day 22 ± 3 Days	Day 1	Day 15[a]		30-35 Days After EOT	Every 8 Weeks	Every 12 Weeks
Informed consent	7.1	X										
Review inclusion/exclusion criteria	3	X										
Demography and medical history	7.3.1	X										
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	X	X		
Physical examination/body weight[b]	7.4.2, 7.4.3	X	X	X	X	X	X	X	X	X		
Vital signs	7.4.4	X	X	X	X	X	X	X	X	X		
12-lead ECG[c]	7.4.5	X	X[c]		X[c]		X		X			
Laboratory tests	7.4.6	X	X	X	X	X	X	X	X	X		
ECOG status	7.6	X	X				X		X	X		
MM disease assessment[d]	7.4.6.8, 7.5.2	X	X				X		X			
Bone marrow examination[e]	7.5.4	X	X (confirming CR)									
Skeletal survey[f]	7.5.6	X	X (investigator discretion)									
Tumor tissue biopsy[g]	7.8.4	X	X									
Buccal swab	7.8.5	X										
Review AEs	7.4.1	X	X	X	X	X	X	X	X	X		
INCB052793 dispensing	7.9.4		X				X					
INCB052793 dose at site[h]	7.9.1		X	X								
Administration of dexamethasone[i]	7.9.7		X	X	X	X	X	X				
Assess compliance	7.9.14		X	X	X	X	X	X	X			
Distribute reminder cards	7.9.15	X	X	X	X	X	X	X	X			
Poststudy disease status	6.4.2										X	
Survival follow-up	6.4.3											X

[a] Day 15 assessments not required from Cycle 4 onward.
[b] Comprehensive physical examination at screening; targeted physical examination thereafter. Body weight will be taken at each visit corresponding with a physical examination. Height will be measured at screening only.
[c] Electrocardiograms will be performed at screening, Day 1 of each cycle, and EOT; triplicate ECGs will be performed predose and 1 and 2 hours postdose on both Cycle 1 Day 1 and Day 15.

[d] Multiple myeloma disease assessments as per Section 7.4.6.8 should be performed at screening, Day 1 of each cycle (± 7 days) for the first 12 months of study participation followed by every 12 weeks (every 3 cycles), and EOT. If the screening MM disease assessment is performed within 7 days of Cycle 1 Day 1, it does not need to be repeated.

[e] A bone marrow examination should be conducted at screening and only if confirming a CR unless otherwise clinically indicated. Fluorescence *in situ* hybridization and cytogenetic testing should be performed when feasible, as per institutional standard.

[f] Skeletal survey should be conducted at screening and subsequently at the discretion of the investigator.

[g] A bone marrow aspirate sample is required at baseline. An optional fresh bone marrow aspirate may be obtained at any time during the study, if a bone marrow examination is otherwise performed to assess disease status.

[h] Study drug will be administered in a fasted state of 2 hours predose and 1 hour postdose with the exception of days with serial PK sampling (Cycle 1 Day 1 and Cycle 1 Day 15), when subjects will fast 8 hours before and 1 hour after study drug administration.

[i] Dexamethasone will be administered at a starting dose of 40 mg administered orally weekly on Days 1, 8, 15, and 22 of each 28-day cycle. Administration should take place in the clinic for all Cycle 1 doses and for all subsequent doses that correspond to a scheduled study visit (ie, Days 1 and 15 of each cycle); all other doses will be self-administered.

Table 7: Laboratory Assessments for Phase 1b/Cohort B Combination Therapy (Dexamethasone)

Local Laboratory Tests	Protocol Section	Screening Phase	Treatment Phase (28-Day Cycles)						EOT	Safety Follow-Up
			Cycle 1				Subsequent Cycles (± 3 Days)			
		Day -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		30-35 Days After EOT
Serum chemistry	7.4.6.1	X	X	X	X	X	X	X	X	X
Hematology[a]	7.4.6.3	X	X	X	X	X	X	X	X	X
Coagulation panel[b]	7.4.6.4	X					X		X	
Urinalysis[b]	7.4.6.5	X					X		X	
Hepatitis serology	7.4.6.7	X								
Central Laboratory Samples										
Expanded serum chemistry	7.4.6.2	X	X	X	X	X	X	X	X	X
Serum pregnancy[c]	7.4.6.6	X					X		X	
PK plasma trough (predose)[d]	7.7.1		X	X	X					
PK plasma TIMED[e]	7.7.1		X		X					
[redacted]										

[a] INCB052793 and dexamethasone should be held on clinic visit days until after the hematology sample is obtained.
[b] Urinalysis and coagulation panel are required at screening; Cycle 2 Day 1, Cycle 4 Day 1 and every third cycle thereafter (7, 10, etc); and at EOT.
[c] For women of childbearing potential, serum pregnancy testing should be performed at screening, on Day 1 of each cycle (beginning with Cycle 2), and EOT. Local urine pregnancy tests can be done throughout the course of the study at the investigator's discretion.
[d] Predose collection of PK on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15.
[e] Collect PK timed samples at 0.5, 1, 2, 4, and 8 hours after dexamethasone administration. Study drug administration should be simultaneous with dexamethasone dosing at Cycle 1 Day 1 and Cycle 1 Day 15.
[f] Collect before dexamethasone administration on Cycle 1 Day 1. Subsequently, PD plasma samples will be collected on Cycle 2 Day 1, Cycle 4 Day 1, and every fourth cycle thereafter without regard to food or study drug dosing.
[g] Whole blood for biomarkers will be collected on Cycle 1 Day 1 (predose), Cycle 2 Day 1, and Cycle 4 Day 1.

Table 8: Schedule of Assessments for Phase 1b/Cohort C Combination Therapy (Carfilzomib)

Procedure	Protocol Section	Screening Phase	Treatment Phase (± 1 Day)[a] (28-Day Cycles)							EOT	Follow-Up Phase		
											Safety Follow-Up	Disease Follow-Up	Survival Follow-Up
		Day -28 to -1	Day 1	Day 2	Day 8	Day 9	Day 15	Day 16	Day 22[b]		30-35 Days After EOT	Every 8 Weeks	Every 12 Weeks
Informed consent	7.1	X											
Review inclusion/exclusion criteria	3	X	X										
Demography and medical history	7.3.1	X											
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	X	X	X		
Physical examination/body weight[c]	7.4.2, 7.4.3	X	X		X		X[c]		X	X	X		
Vital signs	7.4.4	X	X	X	X	X	X	X	X	X	X		
12-lead ECG[d]	7.4.5	X	X[d]				X[d]			X			
Laboratory tests	7.4.6	X	X		X		X		X	X	X		
ECOG status	7.6	X	X							X	X		
MM disease assessment[e]	7.4.6.8, 7.5.2	X	X							X			
Bone marrow examination[f]	7.5.4	X	X (confirming CR)										
Skeletal survey[g]	7.5.6	X	X (investigator discretion)										
Tumor tissue biopsy[h]	7.8.4	X	X										
Buccal swab	7.8.5	X											
Review AEs	7.4.1	X	X	X	X	X	X	X	X	X	X		
INCB052793 dispensing	7.9.4		X										
INCB052793 dose at site[i,j]	7.9.1		X		X		X						
Administration of carfilzomib[k]	7.9.8		X	X	X	X	X	X					
Administration of dexamethasone[l]	7.9.7		X		X		X		X				
Assess compliance	7.9.14		X		X		X		X	X			
Distribute reminder cards	7.9.15	X	X		X		X			X			
Poststudy disease status	6.4.2											X	
Survival follow-up	6.4.3												X

[a] After 12 treatment cycles, subjects will receive maintenance dosing on Days 1, 2, 15, and 16 of each 28-day cycle. No visits or assessments will be required on Day 8 or 9.
[b] Day 22 assessments are performed in Cycle 1 only.
[c] Comprehensive physical examination at screening; targeted physical examination thereafter. Day 15 physical examination not required from Cycle 4 onward. Body weight will be taken at each visit corresponding with a physical examination. Height will be measured at screening only.
[d] Electrocardiograms will be performed at screening, Day 1 of each cycle, and EOT; triplicate ECGs will be performed predose and 1 and 2 hours postdose on both Cycle 1 Day 1 and Day 15.

[e] Multiple myeloma disease assessments as per Section 7.4.6.8 should be performed at screening, Day 1 of each cycle (± 7 days), and EOT. If screening MM disease assessment is performed within 7 days of Cycle 1 Day 1, it does not need to be repeated.

[f] A bone marrow examination should be conducted at screening and only if confirming a CR unless otherwise clinically indicated. Fluorescence *in situ* hybridization and cytogenetic testing should be performed, when feasible, as per institutional standard.

[g] Skeletal survey should be conducted at screening and subsequently at the discretion of the investigator.

[h] A bone marrow aspirate sample is required at baseline. An optional fresh bone marrow aspirate may be obtained at any time during the study, if a bone marrow examination is otherwise performed to assess disease status.

[i] Study drug will be self-administered in a fasted state of 2 hours predose and 1 hour postdose with the exception of days with serial PK sampling (Cycle 1 Day 1 and Cycle 1 Day 15), when subjects will fast 8 hours before and 1 hour after study drug administration.

[j] Dosing at site only required during Cycle 1.

[k] Carfilzomib will be administered on Days 1, 2, 8, 9, 15, and 16 of each 28-day treatment cycle as specified in Section 5.1.2.5. From Cycle 4 onward, subjects are only required to receive carfilzomib at the investigative site on Day 1 of each cycle. All other carfilzomib doses and study assessments may be performed at a local clinic. Data from local clinic assessments do not need to be entered into the CRF.

[l] If disease progression occurs after 1 or more cycles or if a response has not been achieved after 4 cycles (ie, stable disease), dexamethasone 40 mg self-administered orally weekly (Days 1, 8, 15, and 22 of each cycle) may be added to the regimen and continued until study withdrawal.

Table 9: Laboratory Assessments for Phase 1b/Cohort C Combination Therapy (Carfilzomib)

Local Laboratory Tests	Protocol Section	Screening Phase	Treatment Phase (28-Day Cycles)				EOT	Safety Follow-Up
		Day -28 to -1	Day 1	Day 8	Day 15	Day 22[a]		30-35 Days After EOT
Serum chemistry	7.4.6.1	X	X	X	X	X	X	X
Hematology[b]	7.4.6.3	X	X	X	X	X	X	X
Coagulation panel[c]	7.4.6.4	X	X[c]				X	
Urinalysis[c]	7.4.6.5	X	X[c]				X	
Hepatitis serology	7.4.6.7	X						
Central Laboratory Samples								
Expanded serum chemistry	7.4.6.2	X	X	X	X	X	X	X
Serum pregnancy[d]	7.4.6.6	X	X				X	
PK plasma trough (predose)[e]	7.7.1		X	X	X			
PK plasma TIMED[f]	7.7.1		X		X			
[redacted]								

[a] Day 22 assessments are performed in Cycle 1 only; visit window is ± 2 days.
[b] INCB052793 and carfilzomib should be held on clinic visit days until after the hematology sample is obtained.
[c] Urinalysis and coagulation panel are required at screening; Cycle 2 Day 1, Cycle 4 Day 1, and every third cycle thereafter (Cycle 7, 10, etc); and at EOT.
[d] For women of childbearing potential, serum pregnancy testing should be performed at screening, Day 1 of each cycle (beginning with Cycle 2), and EOT. Local urine pregnancy tests can be done throughout the course of the study at the investigator's discretion.
[e] Predose collection of PK on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15.
[f] Collect PK timed samples at 5 minutes, 0.5, 1, 2, 4, and 8 hours after the end of the carfilzomib administration. Study drug dose should be simultaneous with the beginning of the carfilzomib administration at Cycle 1 Day 1 and Cycle 1 Day 15.
[redacted]

Table 10: Schedule of Assessments for Phase 1b/Cohort D Combination Therapy (Bortezomib)

Procedure	Protocol Section	Screening Phase	Treatment Phase Cycles 1-8 (21-Day Cycles) (± 2 Days)[a]				Maintenance Phase[b] (± 3 Days)	EOT	Follow-Up Phase		
									Safety Follow-Up	Disease Follow-Up	Survival Follow-Up
		Day -28 to -1	Day 1	Day 4	Day 8	Day 11	Every 2 Weeks		30-35 Days After EOT	Every 8 Weeks	Every 12 Weeks
Informed consent	7.1	X									
Review inclusion/exclusion criteria	3	X									
Demography and medical history	7.3.1	X									
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	X		
Physical examination/body weight[c]	7.4.2, 7.4.3	X	X		X[c]		X	X	X		
Vital signs	7.4.4	X	X	X	X	X	X	X	X		
12-lead ECG[d]	7.4.5	X	X		X		X	X			
Laboratory tests	7.4.6	X	X	X	X	X	X	X	X		
ECOG status	7.6	X	X				X	X	X		
MM disease assessment[e]	7.4.6.8, 7.5.2	X	X				X	X			
Bone marrow examination[f]	7.5.4	X	X (confirming CR)								
Skeletal survey[g]	7.5.6	X	X (investigator discretion)								
Tumor tissue biopsy[h]	7.8.4	X	X								
Buccal swab	7.8.5	X									
Review AEs	7.4.1	X	X	X	X	X	X	X	X		
INCB052793 dispensing	7.9.4		X				X				
INCB052793 dose at site[i,j]	7.9.1		X		X						
Administration of bortezomib[k]	7.9.9		X	X	X	X	X				
Administration of dexamethasone[l]	7.9.7		X		X		X				
Assess compliance	7.9.14			X	X	X	X				
Distribute reminder cards	7.9.15	X	X	X	X	X	X	X			
Poststudy disease status	6.4.2									X	
Survival follow-up	6.4.3										X

[a] From Cycle 4 onward, subjects are only required to receive bortezomib at the investigative site on Day 1 of each cycle. All other bortezomib doses and study assessments may be performed at a local clinic. Data from local clinic assessments do not need to be entered into the CRF.

[b] After 8 cycles of bortezomib, subjects may initiate maintenance dosing at a schedule of once every 2 weeks, as per Section 5.1.2.6.

[c] Comprehensive physical examination at screening; targeted physical examination thereafter. Day 8 physical examination is not required from Cycle 4 onward. Body weight will be taken at each visit corresponding with a physical examination. Height will be measured at screening only.
[d] Electrocardiograms will be performed at screening, Day 1 of each cycle, and EOT; triplicate ECGs will be performed predose and 1 and 2 hours postdose on both Cycle 1 Day 1 and Day 8.
[e] Multiple myeloma disease assessments as per Section 7.4.6.8 should be performed at screening, Day 1 of each cycle, every 4 weeks during the maintenance phase, and EOT. If screening MM disease assessment is performed within 7 days of Cycle 1 Day 1, it does not need to be repeated.
[f] A bone marrow examination should be conducted at screening and only if confirming a CR unless otherwise clinically indicated. Fluorescence *in situ* hybridization and cytogenetic testing should be performed, when feasible, as per institutional standard.
[g] Skeletal survey should be conducted at screening and subsequently at the discretion of the investigator.
[h] A bone marrow aspirate sample is required at baseline. An optional fresh bone marrow aspirate may be obtained at any time during the study, if a bone marrow examination is otherwise performed to assess disease status.
[i] Study drug will be self-administered in a fasted state of 2 hours predose and 1 hour postdose with the exception of days with serial PK sampling (Cycle 1 Day 1 and Cycle 1 Day 8), when subjects will fast 8 hours before and 1 hour after study drug administration.
[j] Dosing at site only required during Cycle 1.
[k] Bortezomib will be administered on Days 1, 4, 8, and 11 of each 21-day treatment cycle for up to 8 cycles as specified in Section 5.1.2.6. Subsequently, subjects may transition to maintenance dosing every other week.
[l] If disease progression occurs after 1 or more cycles or if a response has not been achieved after 4 cycles (ie, stable disease), dexamethasone at 40 mg self-administered orally weekly (Day 1, Day 8, and Day 15 of each cycle) may be added to the regimen and continued until study withdrawal.

Table 11: Laboratory Assessments for Phase 1b/Cohort D Combination Therapy (Bortezomib)

Local Laboratory Tests	Protocol Section	Screening Phase	Treatment Phase (Cycles 1-8) (21-Day Cycles)				Maintenance Phase	EOT	Safety Follow-Up
		Day -28 to -1	Day 1	Day 4	Day 8	Day 11	Every 2 Weeks		30-35 Days After EOT
Serum chemistry	7.4.6.1	X	X	X	X	X	X	X	X
Hematology[a]	7.4.6.3	X	X	X	X	X	X	X	X
Coagulation panel[b]	7.4.6.4	X	X				X	X	
Urinalysis[b]	7.4.6.5	X	X				X	X	
Hepatitis serology	7.4.6.7	X							
Central Laboratory Samples									
Expanded serum chemistry	7.4.6.2	X	X		X		X	X	X
Serum pregnancy[c]	7.4.6.6	X	X				X	X	
PK plasma trough (predose)[d]	7.7.1		X		X				
PK plasma TIMED[e]	7.7.1		X		X				
[redacted]									

[a] INCB052793 and bortezomib should be held on clinic visit days until after the hematology sample is obtained.
[b] Urinalysis and coagulation panel are required at screening, Cycle 2 Day 1, Cycle 4 Day 1, and every third cycle thereafter (Cycles 7, 10, etc) during the treatment phase and every 6 weeks during the maintenance phase; and at EOT.
[c] For women of childbearing potential, serum pregnancy testing should be performed at screening, Day 1 of each cycle (beginning with Cycle 2) during the treatment phase, every 6 weeks during the maintenance phase, and EOT. Local urine pregnancy tests can be done throughout the course of the study at the investigator's discretion.
[d] Predose collection of PK trough on Cycle 1 Day 1 and Cycle 1 Day 8.
[e] Collect PK timed samples at 5 minutes, 0.5, 1, 2, 4, 6, and 8 hours after bortezomib administration. Study drug should be administered immediately before the bortezomib dose at Cycle 1 Day 1 and Cycle 1 Day 8.

[redacted]

Table 12: Schedule of Assessments for Phase 1b/Cohort E Combination Therapy (Lenalidomide)

Procedure	Protocol Section	Screening Phase	Treatment Phase (28-Day Cycles)						EOT	Follow-Up Phase		
			Cycle 1				Subsequent Cycles (± 3 Days)			Safety Follow-Up	Disease Follow-Up	Survival Follow-Up
		Day -28 to -1	Day 1	Day 8 ± 3 Days	Day 15 ± 3 Days	Day 22 ± 3 Days	Day 1	Day 15[a]		30-35 Days After EOT	Every 8 Weeks	Every 12 Weeks
Informed consent	7.1	X										
Review inclusion/exclusion criteria	3	X										
Demography and medical history	7.3.1	X										
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	X	X		
Physical examination/body weight[b]	7.4.2, 7.4.3	X	X	X	X	X	X	X	X	X		
Vital signs	7.4.4	X	X	X	X	X	X	X	X	X		
12-lead ECG[c]	7.4.5	X	X[b]		X[b]		X		X			
Laboratory tests	7.4.6	X	X	X	X	X	X	X	X	X		
ECOG status	7.6	X	X				X		X	X		
MM disease assessment[d]	7.4.6.8, 7.5.2	X	X				X		X			
Bone marrow examination[e]	7.5.4	X	X (confirming CR)									
Skeletal survey[f]	7.5.6	X	X (investigator discretion)									
Tumor tissue biopsy[g]	7.8.4	X	X									
Buccal swab	7.8.5	X										
Review AEs	7.4.1	X	X	X	X	X	X	X	X	X		
INCB052793 dispensing	7.9.4		X				X					
INCB052793 dose at site[h]	7.9.1		X	X	X							
Administration of lenalidomide at site[i]	7.9.10		X	X	X							
Administration of dexamethasone[j]	7.9.7		X	X	X	X	X	X				
Assess compliance	7.9.14		X	X	X	X	X	X	X			
Distribute reminder cards	7.9.15	X	X	X	X	X	X	X	X			
Poststudy disease status	6.4.2										X	
Survival follow-up	6.4.3											X

[a] Day 15 assessments not required from Cycle 4 onward.

[b] Comprehensive physical examination at screening; targeted physical examination thereafter. Body weight will be taken at each visit corresponding with a physical examination. Height will be measured at screening only.

[c] Electrocardiograms will be performed at screening, Day 1 of each cycle, and EOT; triplicate ECGs will be performed predose and 1 and 2 hours postdose on both Cycle 1 Day 1 and Day 15.
[d] Multiple myeloma disease assessments as per Section 7.4.6.8 should be performed at screening, Day 1 of each cycle (± 7 days), and EOT. If screening MM disease assessment is performed within 7 days of Cycle 1 Day 1, it does not need to be repeated.
[e] A bone marrow examination should be conducted at screening and only if confirming a CR unless otherwise clinically indicated. Fluorescence *in situ* hybridization and cytogenetic testing should be performed, when feasible, as per institutional standard.
[f] Skeletal survey should be conducted at screening and subsequently at the discretion of the investigator.
[g] A bone marrow aspirate sample is required at baseline. An optional fresh bone marrow aspirate may be obtained at any time during the study, if a bone marrow examination is otherwise performed to assess disease status.
[h] Study drug will be administered in a fasted state of 2 hours predose and 1 hour postdose with the exception of days with serial PK sampling (Cycle 1 Day 1 and Cycle 1 Day 15), when subjects will fast 8 hours before and 1 hour after study drug administration.
[i] Lenalidomide will be administered orally QD on Days 1 to 21 of each 28-day cycle, as per Section 5.1.2.7. Administration should take place in the clinic for all Cycle 1 doses (ie, Cycle 1 Day 1, Day 8, and Day 15); all other doses will be self-administered.
[j] If disease progression occurs after 1 or more cycles or if a response has not been achieved after 4 cycles (ie, stable disease), dexamethasone at 40 mg self-administered orally weekly (Days 1, 8, 15, and 22) may be added to the regimen and continued until study withdrawal.

Table 13: Laboratory Assessments for Phase 1b/Cohort E Combination Therapy (Lenalidomide)

Local Laboratory Tests	Protocol Section	Screening Phase	Treatment Phase (28-Day Cycles)						EOT	Safety Follow-Up
			Cycle 1				Subsequent Cycles (± 3 Days)			
		Day -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		30-35 Days After EOT
Serum chemistry	7.4.6.1	X	X	X	X	X	X	X	X	X
Hematology[a]	7.4.6.3	X	X	X	X	X	X	X	X	X
Coagulation panel[b]	7.4.6.4	X					X		X	
Urinalysis[b]	7.4.6.5	X					X		X	
Hepatitis serology	7.4.6.7	X								
Central Laboratory Samples										
Expanded serum chemistry	7.4.6.2	X	X	X	X	X	X	X	X	X
Serum/urine pregnancy[c]	7.4.6.6	X	X	X	X	X	X		X	
PK plasma trough (predose)[d]	7.7.1		X	X	X					
PK plasma TIMED[e]	7.7.1		X		X					
[redacted]										

[a] INCB052793 and lenalidomide should be held on clinic visit days until after the hematology sample is obtained.
[b] Urinalysis and coagulation panel are required at screening; Cycle 2 Day 1, Cycle 4 Day 1, and every third cycle thereafter (Cycles 7, 10, etc); and at EOT.
[c] For women of childbearing potential, serum pregnancy testing will be performed 10 to 14 days before the anticipated initiation of treatment, weekly during Cycle 1, on Day 1 of each cycle (beginning with Cycle 2), and EOT. Local urine pregnancy tests are required at Cycle 1 Day 1 and may be repeated throughout the course of the study at the investigator's discretion.
[d] Predose collection of PK on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15.
[e] Collect PK timed samples at 0.5, 1, 2, 4, and 8 hours after lenalidomide administration. Study drug administration should be simultaneous with lenalidomide dosing at Cycle 1 Day 1 and Cycle 1 Day 15.

[redacted]

Table 14: Schedule of Assessments for Phase 1b/Cohort F Combination Therapy (Azacitidine)

Procedure	Protocol Section	Screening Phase	Treatment Phase (All Cycles) (± 1 Day) (28-Day Cycles)[a]									EOT	Follow-Up Phase		
													Safety Follow-Up	Disease Follow-Up	Survival Follow-Up
		Day -28 to -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 9	Day 15	Day 22[b]		30-35 Days After EOT	Every 8 Weeks	Every 12 Weeks
Informed consent	7.1	X													
Review inclusion/exclusion criteria	3	X													
Demography and medical history	7.3.1	X													
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	X	X	X	X	X		
Physical examination/body weight[c]	7.4.2, 7.4.3	X	X					X[c]		X[c]	X	X	X		
Vital signs	7.4.4	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG[d]	7.4.5	X	X[d]				X[d]					X			
Laboratory tests	7.4.6	X	X				X	X		X	X	X	X		
ECOG status	7.6	X	X									X	X		
AML/MDS disease assessment[e]	7.5.2	X	X									X			
Bone marrow examination[f]	7.5.4	X													
Immunophenotyping[g]	7.5.5	X	X (confirming CR)												
Tumor tissue biopsy[h]	7.8.4	X	X												
Buccal swab	7.8.5	X													
Review AEs	7.4.1	X	X	X	X	X	X	X	X	X	X	X	X		
INCB052793 dispensing	7.9.4		X												
INCB052793 dose at site[i]	7.9.1		X				X								
Administration of azacitidine[j]	7.9.11		X	X	X	X	X	X	X						
Assess compliance	7.9.14		X						X	X	X	X			
Distribute reminder cards	7.9.15	X	X						X	X	X	X	X		
Poststudy disease status	6.4.2													X	
Survival follow-up	6.4.3														X

[a] From Cycle 4 onward, subjects are only required to receive azacitidine at the investigative site on Day 1 of each cycle. All other azacitidine doses and study assessments may be performed at a local clinic. Day 15 assessments are not required beginning with Cycle 4. Data from local clinic assessments do not need to be entered into the CRF.

[b] Day 22 assessments are performed in Cycle 1 only.

[c] Comprehensive physical examination at screening; targeted physical examination thereafter. Day 8 and 15 physical examination is not required from Cycle 4 onward. Body weight will be taken at each visit corresponding with a physical examination. Height will be measured at screening only.

[d] Electrocardiograms will be performed at screening, Days 1 and 5 of Cycle 1, Day 1 of each subsequent cycle, and EOT; triplicate ECGs will be performed predose and 1 and 2 hours postdose on both Cycle 1 Day 1 and Day 5.

[e] AML/MDS response assessments should be performed at screening, on Day 1 (± 7 days) of each cycle for the first 12 months of the study participation followed by every 12 weeks (every 3 cycles), and EOT. If screening disease assessment is performed within 7 days of Cycle 1 Day 1, it does not need to be repeated.

[f] A bone marrow examination will be conducted approximately 3, 6, and 12 months after Day 1 and then every 12 months on the nearest Cycle Day 1 (± 2 days) after the first dose of treatment and as clinically indicated. Fluorescence *in situ* hybridization and cytogenetic testing should be performed, when feasible, as per institutional standard.

[g] Immunophenotyping should be performed at screening, Cycle 2 Day 1, and to confirm a CR.

[h] A bone marrow aspirate sample is required at baseline. An optional fresh bone marrow aspirate may be obtained at any time during the study, if a bone marrow examination is otherwise performed to assess disease status.

[i] Study drug will be self-administered in a fasted state of 2 hours predose and 1 hour postdose with the exception of days with serial PK sampling (Cycle 1 Day 1 and Cycle 1 Day 5), when subjects will fast 8 hours before and 1 hour after study drug administration in the clinic.

[j] Azacitidine will be administered at a dose of 75 mg/m^2 SC for 5 days, followed by 2 days of no treatment, then 75 mg/m^2 for 2 days of each 28-day treatment cycle. Intravenous administration is allowed if SC administration is not tolerated.

[k] After 12 months of study participation, study assessments are conducted every 12 weeks/3 cycles.

Table 15: Laboratory Assessments for Phase 1b/Cohort F Combination Therapy (Azacitidine)

Local Laboratory Tests	Protocol Section	Screening Phase	Treatment Phase (28-Day Cycles)					EOT	Safety Follow-Up
		Day -28 to -1	Day 1	Day 5	Day 8	Day 15	Day 22[a]		30-35 Days After EOT
Serum chemistry	7.4.6.1	X	X	X	X	X	X	X	X
Hematology[b]	7.4.6.3	X	X	X	X	X	X	X	X
Coagulation panel[c]	7.4.6.4	X	X[c]					X	
Urinalysis[c]	7.4.6.5	X	X[c]					X	
Hepatitis serology	7.4.6.7	X							
Central Laboratory Samples									
Expanded serum chemistry	7.4.6.2	X	X	X	X	X	X	X	X
Serum pregnancy[d]	7.4.6.6	X	X					X	
PK plasma trough (predose)[e]	7.7.1		X	X					
PK plasma TIMED[f]	7.7.1		X	X					
[redacted]									

[a] Day 22 assessments are performed in Cycle 1 only; visit window is ± 2 days.
[b] INCB052793 and azacitidine should be held on clinic visit days until after the hematology sample is obtained.
[c] Urinalysis and coagulation panel are required at screening; Cycle 2 Day 1, Cycle 4 Day 1, and every third cycle thereafter (Cycles 7, 10, etc); and at EOT.
[d] For women of childbearing potential, serum pregnancy testing should be performed at screening, Day 1 of each cycle (beginning with Cycle 2), and EOT. Local urine pregnancy tests can be done throughout the course of the study at the investigator's discretion.
[e] Predose collection of PK on Cycle 1 Day 1 and Cycle 1 Day 5.
[f] Collect PK timed samples at 5 minutes, 0.5, 1, 2, 4, and 8 hours after azacitidine administration. Study drug dose should be simultaneous with the beginning of the azacitidine administration at Cycle 1 Day 1 and Cycle 1 Day 5.
[redacted]

Table 16: Schedule of Assessments for Phase 1b/Cohort G Combination Therapy (Pomalidomide/Dexamethasone)

Procedure	Protocol Section	Screening Phase	Treatment Phase (28-Day Cycles)						EOT	Follow-Up Phase		
			Cycle 1				Subsequent Cycles (± 3 Days)			Safety Follow-Up	Disease Follow-Up	Survival Follow-Up
		Day -28 to -1	Day 1	Day 8 ± 3 Days	Day 15 ± 3 Days	Day 22 ± 3 Days	Day 1	Day 15[a]		30-35 Days After EOT	Every 8 Weeks	Every 12 Weeks
Informed consent	7.1	X										
Review inclusion/exclusion criteria	3	X										
Demography and medical history	7.3.1	X										
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	X	X		
Physical examination/body weight[b]	7.4.2, 7.4.3	X	X	X	X		X	X	X	X		
Vital signs	7.4.4	X	X	X	X	X	X	X	X	X		
12-lead ECG[c]	7.4.5	X	X[b]		X[b]		X		X			
Laboratory tests	7.4.6	X	X	X	X	X	X	X	X	X		
ECOG status	7.6	X	X				X		X	X		
MM disease assessment[d]	7.4.6.8, 7.5.2	X	X				X		X			
Bone marrow examination[e]	7.5.4	X	X (confirming CR)									
Skeletal survey[f]	7.5.6	X	X (investigator discretion)									
Tumor tissue biopsy[g]	7.8.4	X	X									
Buccal swab	7.8.5	X										
Review AEs	7.4.1	X	X	X	X	X	X	X	X	X		
INCB052793 dispensing	7.9.4		X				X					
INCB052793 dose at site[h]	7.9.1		X	X	X							
Administration of pomalidomide at site[i]	7.9.12		X		X							
Administration of dexamethasone at site[j]	7.9.7		X	X	X	X						
Assess compliance	7.9.14		X	X	X	X	X	X	X			
Distribute reminder cards	7.9.15	X	X	X	X	X	X	X	X			
Poststudy disease status	6.4.2										X	X
Survival follow-up	6.4.3											X

[a] Day 15 assessments not required from Cycle 4 onward.
[b] Comprehensive physical examination at screening; targeted physical examination thereafter. Body weight will be taken at each visit corresponding with a physical examination. Height will be measured at screening only.

[c] Electrocardiograms will be performed at screening, Day 1 of each cycle, and EOT; triplicate ECGs will be performed predose and 1 and 2 hours postdose on both Cycle 1 Day 1 and Day 15.
[d] Multiple myeloma disease assessments as per Section 7.4.6.8 should be performed at screening, Day 1 of each cycle (± 7 days), and EOT. If screening MM disease assessment is performed within 7 days of Cycle 1 Day 1, it does not need to be repeated.
[e] A bone marrow examination should be conducted at screening and only if confirming a CR unless otherwise clinically indicated. Fluorescence *in situ* hybridization and cytogenetic testing should be performed, when feasible, as per institutional standard.
[f] Skeletal survey should be conducted at screening and subsequently at the discretion of the investigator.
[g] A bone marrow aspirate sample is required at baseline. A fresh bone marrow examination (including aspirate) must be performed before first study drug dose. An optional bone marrow aspirate may be obtained at any time during the study, if a bone marrow examination is otherwise performed to assess disease status.
[h] Study drug will be administered in a fasted state of 2 hours predose and 1 hour postdose with the exception of days with serial PK sampling (Cycle 1 Day 1 and Cycle 1 Day 15), when subjects will fast 8 hours before and 1 hour after study drug administration.
[i] Pomalidomide will be administered orally QD on Days 1 to 21 of each 28-day cycle, as per Section 5.1.2.9. Administration should take place in the clinic at Cycle 1 Day 1, and Day 15; all other doses will be self-administered.
[j] Dexamethasone will be administered at a starting dose of 40 mg orally on a weekly basis on study Days 1, 8, 15, and 22 of each 28-day cycle. Administration should take place in the clinic at Cycle 1 Day 1, Day 8, Day 15, and Day 22; all other doses will be self-administered.

Table 17: Laboratory Assessments for Phase 1b/Cohort G Combination Therapy (Pomalidomide/Dexamethasone)

Local Laboratory Tests	Protocol Section	Screening Phase	Treatment Phase (28-Day Cycles)						EOT	Safety Follow-Up
			Cycle 1				Subsequent Cycles (± 3 Days)			
		Day -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15		30-35 Days After EOT
Serum chemistry	7.4.6.1	X	X	X	X	X	X	X	X	X
Hematology[a]	7.4.6.3	X	X	X	X	X	X	X	X	X
Coagulation panel[b]	7.4.6.4	X					X		X	
Urinalysis[b]	7.4.6.5	X					X		X	
Hepatitis serology	7.4.6.7	X								
Central Laboratory Samples										
Expanded serum chemistry	7.4.6.2	X	X	X	X	X	X	X	X	X
Serum/urine pregnancy[c]	7.4.6.6	X	X	X	X	X	X		X	
PK plasma trough (predose)[d]	7.7.1		X	X	X					
PK plasma TIMED[e]	7.7.1		X		X					
[redacted]										

[a] INCB052793, pomalidomide, and dexamethasone should be held on clinic visit days until after the hematology sample is obtained.
[b] Urinalysis and coagulation panel are required at screening; Cycle 2 Day 1, Cycle 4 Day 1, and every third cycle thereafter (Cycles 7, 10, etc); and at EOT.
[c] For women of childbearing potential, serum pregnancy testing will be performed 10 to 14 days before the anticipated initiation of treatment, weekly during Cycle 1, on Day 1 of each cycle (beginning with Cycle 2), and EOT. Local urine pregnancy tests are required at Cycle 1 Day 1 and may be repeated throughout the course of the study at the investigator's discretion.
[d] Predose collection of PK on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15.
[e] Collect PK timed samples at 0.5, 1, 2, 4, and 8 hours after pomalidomide administration. Study drug administration should be simultaneous with pomalidomide dosing at Cycle 1 Day 1 and Cycle 1 Day 15.
[redacted]

Table 18: Schedule of Assessments for Phase 1b/Cohort H Combination Therapy (INCB052793 + INCB050465)

Procedure	Protocol Section	Screening	Treatment Phase (21-Day Cycles)				EOT	Follow-Up Phase		
			Cycle 1			Subsequent Cycles		Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up
		Day -28 to -1	Day 1	Day 8 ± 3 Days	Day 15 ± 3 Days	Day 1 ± 3 Days		30-35 Days After EOT[a]	Every 8 Weeks (± 7 Days) After EOT	Every 12 Weeks (± 7 Days)
Informed consent	7.1	X								
Review inclusion/ exclusion criteria	3	X								
Demography and medical history	7.3.1	X								
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X		
Physical examination/body weight[b]	7.4.2 7.4.3	X	X	X	X	X	X	X		
Vital signs	7.4.4	X	X	X	X	X	X	X		
ECOG status	7.6	X	X			X	X	X		
12-lead ECG[c]	7.4.5	X	X		X	X	X			
Laboratory tests	7.4.6	X	X	X	X	X	X	X[c]		
Bone marrow examination[d]	7.5.4	X								
Lymph node biopsy/archival tissue[e]	7.8.4	X	X							
Buccal swab	7.8.5	X								
Efficacy/disease assessment[f]	7.5.2 7.5.3	X								
Review of AEs	7.4.1	X	X	X	X	X	X	X		
INCB052793 administer in clinic[g]	7.9.1		X	X	X					
INCB050465 administer in clinic[g]	7.9.2		X	X	X					
Assess compliance	7.9.14		X	X	X	X	X			
Distribute reminder cards	7.9.15	X	X	X	X	X	X			
Poststudy disease status	6.4.2								X	
Survival follow-up	6.4.3									X

[a] In addition to laboratory assessments at the safety follow-up visit, serum (1,3)-β-D-glucan will be assessed at 3 months ± 1 week after EOT.
[b] Comprehensive physical examination at screening; targeted physical examination thereafter. Body weight will be taken at each visit. Height is measured at screening only.
[c] Electrocardiograms will be performed at screening, Day 1 of each cycle, and EOT; timed triplicate ECGs will be performed predose and 1 and 2 hours postdose on Cycle 1 Day 1 and Day 15. The ECGs should be conducted before, but within 15 minutes of, the PK blood draw at the corresponding timepoint.
[d] A bone marrow biopsy will be performed on all subjects at screening (with exceptions noted) as outlined in Section 7.5.4.

[e] A lymph node biopsy for genetic material will be collected on all subjects at screening. Archival tissue may be submitted if available and if criteria in Section 7.8.4 are met (eg, archival tissue obtained after completion of last treatment regimen). If a biopsy is performed during the treatment phase to assess disease status, to confirm response or progression, or if otherwise clinically indicated, a sample of the biopsy will optionally be provided to the sponsor.

[f] Computed tomography, MRI, FDG-PET, and/or PET/CT (appropriate to histology) will be conducted every 6 weeks (every 2 cycles) until the subject enters into the disease status follow-up phase. Treatment cycles may be delayed; therefore, tumor assessments may be delayed as well to synchronize with treatment cycles regardless if treatment is delayed due to safety (± 10-day window). For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status, including, if applicable, radiographic disease imaging until 1) start of new anticancer therapy, 2) documented disease progression, 3) death, or 4) the end of study, whichever comes first.

[g] Study drug will be administered in a fasted state of 2 hours predose and 1 hour postdose with the following exception: On days with PK [redacted] sampling, subjects will fast 8 hours before and 1 hour after study drug administration. Study drug should be administered in the clinic on days where there are PK [redacted] collections as outlined in Sections 7.7.1 and 7.8. Otherwise, the study drug will be self-administered by the subject.

Table 19: Laboratory Assessments Phase 1b/Cohort H Combination Therapy (INCB052793 + INCB050465)

Local Laboratory Tests	Protocol Section	Screening Phase	Treatment Phase (21-Day Cycles)				EOT	Safety Follow-Up
			Cycle 1			Subsequent Cycles (± 3 Days)		
		Day -28 to -1	Day 1	Day 8 ± 3 Days	Day 15 ± 3 Days	Day 1		30-35 Days After EOT
Serum chemistry	7.4.6.1	X	X	X	X	X	X	X
Hematology[a]	7.4.6.3	X	X	X	X	X	X	X
Coagulation panel[b]	7.4.6.4	X				X	X	
Urinalysis[b]	7.4.6.5	X				X	X	
Hepatitis serology	7.4.6.7	X						
Central Laboratory Samples								
Serum (1,3)-β-D-glucan[c]		X				X	X	X
Expanded serum chemistry	7.4.6.2	X	X			X	X	X
Serum/urine pregnancy[d]	7.4.6.6	X				X	X	
PK TIMED[e, f]	7.7.1		X		X			
[redacted]								

[a] INCB052793 and INCB050465 should be held on clinic visit days until after the hematology sample is obtained.
[b] Urinalysis and coagulation panel are required at screening, Cycle 2 Day 1, Cycle 4 Day 1, and every third cycle thereafter (Cycles 7, 10, etc); and at EOT.
[c] Serum (1,3)-β-D-glucan required at Day 1 of each cycle (from Cycle 2 onward), EOT, safety follow-up, and at 3 months ± 1 week after EOT.
[d] For women of childbearing potential, serum pregnancy testing should be performed at screening, Day 1 of each cycle (beginning with Cycle 2), and EOT. Local urine pregnancy tests can be done throughout the course of the study at the investigator's discretion.
[e] Day 1 and Day 15 (predose) and timed PK (see footnote f). Collect trough before morning dose of study drug. Study drug administration will occur in the clinic. Subjects should refrain from eating 8 hours before arriving at the clinic and 1 hour after study drug administration.
[f] Timed PK: Collect samples predose and 0.5, 1, 2, 4, 6, and 8 hours postdose. Study drug administration will occur in the clinic. Subjects should refrain from eating 8 hours before arriving at the clinic and 1 hour after study drug administration.
[redacted]

Table 20: Schedule of Assessments for Phase 2/Cohort I (INCB052793 With Azacitidine)

Procedure	Protocol Section	Screening Phase	Treatment Phase (All Cycles) (± 1 Day) (28-Day Cycles)[a]									EOT	Follow-Up Phase		
													Safety Follow-Up	Disease Follow-Up	Survival Follow-Up
		Day -28 to -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 9	Day 15	Day 22[b]		30-35 Days After EOT	Every 8 Weeks	Every 12 Weeks
Informed consent	7.1	X													
Review inclusion/exclusion criteria	3	X													
Demography and medical history	7.3.1	X													
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	X	X	X	X	X		
Physical examination/body weight[c]	7.4.2, 7.4.3	X	X					X[c]		X[c]	X	X	X		
Vital signs	7.4.4	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG[d]	7.4.5	X	X[d]				X[d]					X			
Laboratory tests	7.4.6	X	X				X	X		X	X	X	X		
ECOG status	7.6	X	X									X	X		
AML/MDS disease assessment[e]	7.5.2	X	X									X			
Bone marrow examination[f]	7.5.4	X													
Immunophenotyping[g]	7.5.5	X	X (confirming CR)												
Tumor tissue biopsy[h]	7.8.4	X	X												
Buccal swab	7.8.5	X													
Review AEs	7.4.1	X	X	X	X	X	X	X	X	X	X	X	X		
INCB052793 dispensing	7.9.4		X												
INCB052793 dose at site[i]	7.9.1		X				X								
Administration of azacitidine[j]	7.9.11		X	X	X	X	X	X	X						
Assess compliance	7.9.14		X						X	X	X	X			
Distribute reminder cards	7.9.15	X	X						X	X	X	X	X		
Poststudy disease status	6.4.2													X	
Survival follow-up	6.4.3														X

[a] From Cycle 4 onward, subjects are only required to receive azacitidine at the investigative site on Day 1 of each cycle. All other azacitidine doses and study assessments may be performed at a local clinic. Day 15 assessments are not required beginning with Cycle 4. Data from local clinic assessments do not need to be entered into the CRF.

[b] Day 22 assessments are performed in Cycle 1 only.

[c] Comprehensive physical examination at screening; targeted physical examination thereafter. Day 8 and 15 physical examination is not required from Cycle 4 onward. Body weight will be taken at each visit corresponding with a physical examination. Height will be measured at screening only.

[d] Electrocardiograms will be performed at screening, Days 1 and 5 of Cycle 1, Day 1 of each subsequent cycle, and EOT; triplicate ECGs will be performed predose and 1 and 2 hours postdose on both Cycle 1 Day 1 and Day 5.

[e] AML/MDS response assessments should be performed at screening, on Day 1 (± 7 days) of each cycle for the first 12 months of the study participation followed by every 12 weeks (every 3 cycles), and EOT. If screening disease assessment is performed within 7 days of Cycle 1 Day 1, it does not need to be repeated.

[f] A bone marrow examination will be conducted approximately 3, 6, and 12 months after Day 1 and then every 12 months on the nearest Cycle Day 1 (± 2 days) after the first dose of treatment and as clinically indicated. Fluorescence *in situ* hybridization and cytogenetic testing should be performed, when feasible, as per institutional standard.

[g] Immunophenotyping should be performed at screening, Cycle 2 Day 1, and to confirm a CR.

[h] A bone marrow aspirate sample is required at baseline. An optional fresh bone marrow aspirate may be obtained at any time during the study, if a bone marrow examination is otherwise performed to assess disease status.

[i] Study drug will be self-administered in a fasted state of 2 hours predose and 1 hour postdose with the exception of days with serial PK sampling (Cycle 1 Day 1 and Cycle 1 Day 5), when subjects will fast 8 hours before and 1 hour after study drug administration in the clinic.

[j] Azacitidine will be administered at a dose of 75 mg/m^2 SC for 5 days, followed by 2 days of no treatment, then 75 mg/m^2 for 2 days of each 28-day treatment cycle. Intravenous administration is allowed if SC administration is not tolerated.

[k] After 12 months of study participation, study assessments are conducted every 12 weeks/3 cycles.

Table 21: Laboratory Assessments for Phase 2/Cohort I (INCB052793 With Azacitidine)

Local Laboratory Tests	Protocol Section	Screening Phase	Treatment Phase (28-Day Cycles)					EOT	Safety Follow-Up
		Day -28 to -1	Day 1	Day 5	Day 8	Day 15	Day 22[a]		30-35 Days After EOT
Serum chemistry	7.4.6.1	X	X	X	X	X	X	X	X
Hematology[b]	7.4.6.3	X	X	X	X	X	X	X	X
Coagulation panel[c]	7.4.6.4	X	X[c]					X	
Urinalysis[c]	7.4.6.5	X	X[c]					X	
Hepatitis serology	7.4.6.7	X							
Central Laboratory Samples									
Expanded serum chemistry	7.4.6.2	X	X	X	X	X	X	X	X
Serum pregnancy[d]	7.4.6.6	X	X					X	
PK plasma trough (predose)[e]	7.7.1		X	X					
PK plasma TIMED[f]	7.7.1		X	X					
[redacted]									

[a] Day 22 assessments are performed in Cycle 1 only; visit window is ± 2 days.
[b] INCB052793 and azacitidine should be held on clinic visit days until after the hematology sample is obtained.
[c] Urinalysis and coagulation panel are required at screening; Cycle 2 Day 1, Cycle 4 Day 1, and every third cycle thereafter (Cycles 7, 10, etc); and at EOT.
[d] For women of childbearing potential, serum pregnancy testing should be performed at screening, Day 1 of each cycle (beginning with Cycle 2), and EOT. Local urine pregnancy tests can be done throughout the course of the study at the investigator's discretion.
[e] Predose collection of PK on Cycle 1 Day 1 and Cycle 1 Day 5.
[f] Collect PK timed samples at 5 minutes, 0.5, 1, 2, 4, and 8 hours after azacitidine administration. Study drug dose should be simultaneous with the beginning of the azacitidine administration at Cycle 1 Day 1 and Cycle 1 Day 5.
[redacted]

Table 22: Schedule of Assessments for Phase 2/Cohort J (Itacitinib With Azacitidine)

Procedure	Protocol Section	Screening Phase	Treatment Phase (All Cycles) (± 1 Day) (28-Day Cycles)[a]									EOT	Follow-Up Phase		
													Safety Follow-Up	Disease Follow-Up	Survival Follow-Up
		Day -28 to -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 9	Day 15	Day 22[b]		30-35 Days After EOT	Every 8 Weeks	Every 12 Weeks
Informed consent	7.1	X													
Review inclusion/exclusion criteria	3	X													
Demography and medical history	7.3.1	X													
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	X	X	X	X	X		
Physical examination/body weight[c]	7.4.2, 7.4.3	X	X					X[c]		X[c]	X	X	X		
Vital signs	7.4.4	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG[d]	7.4.5	X	X[d]				X[d]					X			
Laboratory tests	7.4.6	X	X				X	X		X	X	X	X		
ECOG status	7.6	X	X									X	X		
AML/MDS disease assessment[e]	7.5.2	X	X									X			
Bone marrow examination[f]	7.5.4	X													
Immunophenotyping[g]	7.5.5	X	X (confirming CR)												
Tumor tissue biopsy[h]	7.8.4	X	X												
Buccal swab	7.8.5	X													
Review AEs	7.4.1	X	X	X	X	X	X	X	X	X	X	X	X		
Itacitinib dispensing	7.9.4		X												
Itacitinib dose at site[i]	7.9.3		X				X								
Administration of azacitidine[i]	7.9.11		X	X	X	X	X	X	X						
Assess compliance	7.9.14		X						X	X	X	X			
Distribute reminder cards	7.9.15	X	X						X	X	X	X	X		
Poststudy disease status	6.4.2													X	
Survival follow-up	6.4.3														X

[a] From Cycle 4 onward, subjects are only required to receive azacitidine at the investigative site on Day 1 of each cycle. All other azacitidine doses and study assessments may be performed at a local clinic. Day 15 assessments are not required beginning with Cycle 4. Data from local clinic assessments do not need to be entered into the CRF.

[b] Day 22 assessments are performed in Cycle 1 only.

[c] Comprehensive physical examination at screening; targeted physical examination thereafter. Day 8 and 15 physical examination is not required from Cycle 4 onward. Body weight will be taken at each visit corresponding with a physical examination. Height will be measured at screening only.

[d] Electrocardiograms will be performed at screening, Days 1 and 5 of Cycle 1, Day 1 of each subsequent cycle, and EOT; triplicate ECGs will be performed predose and 1 and 2 hours postdose on both Cycle 1 Day 1 and Day 5.

[e] AML/MDS response assessments should be performed at screening, on Day 1 (± 7 days) of each cycle for the first 12 months of the study participation followed by every 12 weeks (every 3 cycles), and at EOT. If screening disease assessment is performed within 7 days of Cycle 1 Day 1, it does not need to be repeated.

[f] A bone marrow examination will be conducted approximately 3, 6, and 12 months after Day 1 and then every 12 months on the nearest Cycle Day 1 (± 2 days) after the first dose of treatment and as clinically indicated. Fluorescence *in situ* hybridization and cytogenetic testing should be performed, when feasible, as per institutional standard.

[g] Immunophenotyping should be performed at screening, Cycle 2 Day 1, and to confirm a CR.

[h] A bone marrow aspirate sample is required at baseline. An optional fresh bone marrow aspirate may be obtained at any time during the study, if a bone marrow examination is otherwise performed to assess disease status.

[i] Study drug will be self-administered in a fasted state of 2 hours predose and 1 hour postdose with the exception of days with serial PK sampling (Cycle 1 Day 1 and Cycle 1 Day 5), when subjects will fast 8 hours before and 1 hour after study drug administration in the clinic.

[j] Azacitidine will be administered at a dose of 75 mg/m^2 SC for 5 days, followed by 2 days of no treatment, then 75 mg/m^2 for 2 days of each 28-day treatment cycle. Intravenous administration is allowed if SC administration is not tolerated.

[k] After 12 months of study participation, study assessments are conducted every 12 weeks/3 cycles.

Table 23: Laboratory Assessments for Phase 2/Cohort J (Itacitinib With Azacitidine)

Local Laboratory Tests	Protocol Section	Screening Phase	Treatment Phase (28-Day Cycles)					EOT	Safety Follow-Up
		Day -28 to -1	Day 1	Day 5	Day 8	Day 15	Day 22[a]		30-35 Days After EOT
Serum chemistry	7.4.6.1	X	X	X	X	X	X	X	X
Hematology[b]	7.4.6.3	X	X	X	X	X	X	X	X
Coagulation panel[c]	7.4.6.4	X	X[c]					X	
Urinalysis[c]	7.4.6.5	X	X[c]					X	
Hepatitis serology	7.4.6.7	X							
Central Laboratory Samples									
Expanded serum chemistry	7.4.6.2	X	X	X	X	X	X	X	X
Serum pregnancy[d]	7.4.6.6	X	X					X	
PK plasma trough (predose)[e]	7.7.1		X	X					
PK plasma TIMED[f]	7.7.1		X	X					
[redacted]									

[a] Day 22 assessments are performed in Cycle 1 only; visit window is ± 2 days.
[b] Itacitinib and azacitidine should be held on clinic visit days until after the hematology sample is obtained.
[c] Urinalysis and coagulation panel are required at screening; Cycle 2 Day 1, Cycle 4 Day 1, and every third cycle thereafter (Cycles 7, 10, etc); and at EOT.
[d] For women of childbearing potential, serum pregnancy testing should be performed at screening, Day 1 of each cycle (beginning with Cycle 2), and EOT. Local urine pregnancy tests can be done throughout the course of the study at the investigator's discretion.
[e] Predose collection of PK on Cycle 1 Day 1 and Cycle 1 Day 5.
[f] Collect PK timed samples at 5 minutes, 0.5, 1, 2, 4, and 8 hours after azacitidine administration. Study drug dose should be simultaneous with the beginning of the azacitidine administration at Cycle 1 Day 1 and Cycle 1 Day 5.
[redacted]

Table 24: Laboratory Tests: Required Analytes

<table>
<tr><th>Serum Chemistry</th><th>Serology</th><th>Hematology</th><th>Urinalysis</th><th colspan="2">Coagulation</th></tr>
<tr><td rowspan="2">Albumin
Alkaline phosphatase
ALT
AST
Bicarbonate
Blood urea nitrogen
Calcium
Chloride
Creatinine
Glucose
LDH
Magnesium
Phosphate
Potassium
Sodium
Total bilirubin
Direct (conjugated) bilirubin (required only if total bilirubin is abnormal)
Total serum protein
Total cholesterol
Triglycerides</td><td rowspan="2">Hepatitis B surface antigen
Anti-hepatitis Bc
HBV-DNA
Anti-hepatitis C
HCV-RNA</td><td rowspan="2">Hemoglobin
Hematocrit
Platelet count
Red blood cell count
WBC count
Differential cell count (absolute and %):
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils
• Reticulocytes</td><td rowspan="2">Color/appearance
pH
Specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Blood
Protein
Microscopic analysis</td><td colspan="2">PT
PTT
INR</td></tr>
<tr><td colspan="2">OTHER
MM subjects:
1. Beta-2 microglobulin
2. Serum protein electrophoresis including M-protein quantitation, urine protein electrophoresis including M-protein quantitation, quantitative immunoglobulins, serum free light chains

Lymphoma and AML/MDS Subjects:
Immunophenotyping

Cohort H:
Serum (1,3)-β-D-glucan</td></tr>
<tr><td></td><td></td><td></td><td></td><td>Females Only

Serum pregnancy</td><td>Expanded Serum Chemistries

CRP</td></tr>
</table>

CRP = C-reactive protein; GGT = gamma glutamyl transferase; IgG = immunoglobulin G; INR = international normalized ratio; LDH = lactose dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time.

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

6.1. Screening Phase

The screening phase is the interval between the signing of the ICF and the day the subject is enrolled in the study (Cycle 1 Day 1). Informed consent must be obtained before performing any study-specific procedures. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during this phase. The maximum screening period is 28 days.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before randomization or the administration of study drug on Cycle 1 Day 1 of both Phase 1a monotherapy and Phase 1b and Phase 2 combination therapy. Tests with results that fail eligibility requirements may be repeated once during the screening phase if the investigator believes the results to be in error. 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).

Additionally, baseline assessments of clinical condition and disease status will be determined during the screening phase. Disease assessments appropriate to the type of malignancy will be performed and recorded in the CRF.

6.2. Treatment Phase

Treatment begins on the day that the subject is enrolled in the study and receives the first dose of study drugs; this is defined as Cycle 1 Day 1. Dates for subsequent study visits will be determined based on this day and should occur within the allowable visit window of the scheduled date unless delayed for safety reasons. At Cycle 1 Day 1, results from screening visit evaluations should be reviewed to determine if the subject continues to meet the eligibility requirements as specified in the Protocol.

During the treatment phase, regular study visits (physician visits) will occur weekly during the first treatment cycle (ie, Days 1, 8, and 15 of Cycle 1) and thereafter at the beginning of each 21-day treatment cycle for Phase 1a. For Phase 1b, study visits will occur at the intervals specified in Table 2, Table 4, Table 6, Table 8, Table 10, Table 12, Table 14, Table 16, and Table 18 (as applicable to study phase and treatment cohort). Study visits occurring in Phase 2 are specified in Table 20 and Table 22.

At certain study visits as indicated in Table 2, Table 4, Table 6, Table 8, Table 10, Table 12, Table 14, Table 16, Table 18, Table 20, and Table 22, subjects will have fasted for at least 8 hours, recorded the time of the previous study drug administration and time of last meal, and withheld the dose of the study drug. At these visits, PK [redacted] sampling will be conducted.

6.3. End of Treatment

If a decision is made that the subject will permanently discontinue 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 page in the CRF. The subject should be encouraged to return for the follow-up visits.

6.4. Follow-Up Phase

6.4.1. Safety Follow-Up

The safety follow-up phase is the interval between the EOT visit and the scheduled safety follow-up visit. Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the safety follow-up visit, or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this phase.

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 phase and should be assessed at the intervals specified (± 1 week) in Table 2, Table 4, Table 6, Table 8, Table 10, Table 12, Table 14, Table 16, Table 18, Table 20, and Table 22 (as applicable to study phase and treatment cohort), utilizing the respective disease assessment criteria to monitor disease status. Every effort should be made to collect information regarding disease status until:

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

6.4.3. Survival Follow-Up

Once a subject has confirmed disease progression or starts a new anticancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone, email, or visit at least every 12 weeks (± 1 week) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.5. Unscheduled Visits

Unscheduled visits may occur at any time as medically warranted. Any assessments performed during those visits should be recorded in the CRF.

6.6. Early Termination

The sponsor may terminate the study electively or if required by regulatory decision. If the study is terminated prematurely, the sponsor will notify the investigators, the institutional review boards (IRBs) and/or independent ethics committees (IECs), and regulatory bodies of the decision and the reason for termination of the study.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

Required assessments/procedures listed here will be captured on the CRF.

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures. The granting of informed consent for study participation must be documented in writing, using an ICF that contains all the 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; a copy of the signed ICF must be provided to the study subject. Subjects of childbearing potential must agree to take appropriate measures to avoid pregnancy in order to participate in the study (see Appendix A). Subjects who have standard-of-care procedures performed within a particular time frame outside of the screening window may not have to repeat these procedures, but only with the approval of the sponsor medical monitor.

7.2. Interactive Response Technology Procedure

Not applicable.

7.3. Demography and History

7.3.1. Demographics and Medical History

Demographic data and a complete medical and medication history will be collected at screening. Cohorts that include subjects with MM (Phase 1a/TGA and Phase 1b/Cohorts B through E and G) will also collect up to approximately 3 months of serum/urine m-protein and/or free light chain values (as applicable) that immediately precede the initiation of study treatment. This will include complete documentation of the history of medical or surgical treatment for the malignancy under study.

7.3.2. Prior and Concomitant Medications

Prior and/or ongoing medications will be reviewed during screening to determine study eligibility and will continue to be recorded throughout the duration of the study. The medication record will be maintained following enrollment, including any changes to the dose or regimen. Prior/concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during 30 days before Cycle 1 Day 1 and throughout the study period through safety follow-up.

7.4. Safety Assessments

7.4.1. 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 through the safety follow-up visit. Treatment-emergent AEs will be referred to as AEs that occur

from day of study drug administration. 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 CRFs 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.

7.4.2. Comprehensive Physical Examination

A comprehensive physical examination will be performed at the times indicated in the Schedule of Assessments (Table 2, Table 4, Table 6, Table 8, Table 10, Table 12, Table 14, Table 16, Table 18, Table 20, and Table 22). Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits.

The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; lymph nodes; and a brief neurological examination. The screening assessment should also include a measurement of height and body weight. Body weight should be collected at each visit. Spleen measurements for applicable tumor types may be obtained from either scan or manual measurements. However, the procedure for measurement must remain consistent throughout the study. Measurements will be captured in the CRF.

7.4.3. Targeted Physical Examination

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

7.4.4. Vital Signs

Vital sign measurements (blood pressure, pulse, respiratory rate, and body temperature) will be taken with the subject in the recumbent, semirecumbent, or sitting position after 5 minutes of rest.

7.4.5. Electrocardiograms

Single 12-lead ECGs will be conducted at screening, Day 1 of each cycle, and EOT. In addition, timed ECGs will be conducted in Phase 1a (see Section 7.4.5.1) and Phase 1b and Phase 2 (see Section 7.4.5.2). All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest. The 12-lead ECGs may be interpreted by the investigator at the site and used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Meaningful" is the responsibility of the investigator in consultation with the sponsor's medical monitor, as appropriate. All ECGs will be collected and analyzed centrally.

7.4.5.1. Phase 1a Monotherapy Timed ECG

In both TGA and TGB, triplicate ECGs will be performed predose and 1 and 2 hours postdose on Cycle 1 Day 1 and Cycle 1 Day 15. The third (last) of the triplicate ECGs should be completed

before, but within, 15 minutes of the PK blood draw at the corresponding timepoint, where applicable. Where a timed ECG assessment does not correlate with a PK blood draw, it can be completed within ± 15 minutes of the target timepoint. The specified postdose timepoint may be adjusted based on emerging PK data.

7.4.5.2. Phase 1b and Phase 2 Combination Therapy Timed ECG

Triplicate ECGs will be performed predose and 1 and 2 hours postdose on Cycle 1 Day 1 and Day 15 (Phase 1b Cohorts A, B, C, E, G, and H), Cycle 1 Day 1 and Day 5 (Phase 1b Cohort F and Phase 2 Cohorts I and J), and Cycle 1 Day 1 and Day 8 (Phase 1b Cohort D). The third (last) of the triplicate ECGs should be completed before, but within, 15 minutes of the PK blood draw at the corresponding timepoint, where applicable. Where a timed ECG assessment does not correlate with a PK blood draw, it can be completed within ± 15 minutes of the target timepoint. The specified postdose timepoint may be adjusted based on emerging PK data.

7.4.6. Laboratory Assessments

A laboratory local to the study site and subject may perform all clinical laboratory assessments for safety (eg, serum chemistry and hematology assessments, urinalysis, serology) as well as the MM response and immunophenotyping assessments. A central laboratory will perform the serum pregnancy tests at screening and the expanded serum chemistry testing throughout the study. The investigative site will enter the local safety laboratory results and laboratory normal ranges into the CRF. All local laboratory assessments should be performed using standard procedures on the days indicated in Table 3, Table 5, Table 7, Table 9, Table 11, Table 13, Table 15, Table 17,Table 19, Table 21, and Table 23 (as applicable to study phase and treatment cohort). Table 24 lists the required laboratory tests. Additional tests may be performed if clinically indicated.

7.4.6.1. Chemistry

A panel of standard serum chemistries and expanded serum chemistries will be performed as indicated in Table 3, Table 5, Table 7, Table 9, Table 11, Table 13, Table 15, Table 17, Table 19, Table 21, and Table 23 (as applicable to study phase and treatment cohort); required analytes for this panel are listed in Table 24.

7.4.6.2. Expanded Chemistry

Serum markers of nutritional and systemic inflammatory response status will be performed as outlined in Table 3, Table 5, Table 7, Table 9, Table 11, Table 13, Table 15, Table 17, and Table 19, Table 21, and Table 23 (as applicable to study phase and treatment cohort). A list of required analytes is found in Table 24. Expanded serum chemistries will be performed from blood samples collected without respect to food intake (ie, nonfasted).

7.4.6.3. Hematology

Hematology will be performed as indicated in Table 3, Table 5, Table 7, Table 9, Table 11, Table 13, Table 15, Table 17, Table 19, Table 21, and Table 23 (as applicable to study phase and treatment cohort); required analytes are listed in Table 24. Subjects will take study drug at the

clinic after the hematology sample is drawn on clinic days when a hematology sample is obtained.

7.4.6.4. Coagulation Panel

A coagulation panel including PT and INR will be measured at screening; Cycle 2 Day 1, Cycle 4 Day 1, and every third cycle thereafter (Cycles 7, 10, etc); and EOT. Subjects who are taking anticoagulant therapy will be monitored per local institutional guidelines.

7.4.6.5. Urinalysis

Complete urinalysis will be performed at screening; Cycle 2 Day 1, Cycle 4 Day 1, and every third cycle thereafter (Cycles 7, 10, etc); and at EOT, as indicated in Table 3, Table 5, Table 7, Table 9, Table 11, Table 13, Table 15, Table 17,Table 19, Table 21, and Table 23 (as applicable to study phase and treatment cohort); required analyses are listed in Table 24.

7.4.6.6. Pregnancy Testing

A serum pregnancy test will be required for all female subjects of childbearing potential at screening, Day 1 of each cycle starting with Cycle 2 (Phase 1b and Phase 2), and EOT. Phase 1b/Treatment Cohort E will have weekly serum pregnancy testing performed during Cycle 1. Subsequently, urine pregnancy tests will be conducted only as medically indicated or per country-specific requirements. Urine pregnancy tests will be performed locally.

7.4.6.7. Serology

Serology will be performed on all subjects at screening to rule out hepatitis infection; required analytes are shown in Table 24.

7.4.6.8. Multiple Myeloma Disease Assessment

Multiple myeloma laboratory assessments will include serum protein electrophoresis (including quantitative M-protein), 24-hour urine protein, urine protein electrophoresis (including quantitative M-protein), quantitative immunoglobulins, serum free light chains, and beta-2 microglobulin. Tests samples should be drawn or collected and brought in (24-hour urine) for all of these tests at screening, Day 1 of subsequent cycles for the first 12 months of the study participation followed by every 12 weeks, and EOT to assess for response in MM subjects. For subjects who do not show evidence of urine paraprotein at screening, spot urine with urine protein electrophoresis will only be required, but if the subject subsequently shows evidence of urine paraprotein, a 24-hour collection will be required along with the urine protein electrophoresis. In addition, a bone marrow (aspirate and biopsy) will be required to confirm CR (IMWG criteria, Durie et al 2006, Appendix D).

7.5. Disease Assessments

Treatment cycles may be delayed; therefore, disease assessments may be delayed as well to synchronize with treatment cycles. A disease assessment may be performed as an unscheduled procedure if clinically indicated. For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status until

(1) start of new anticancer therapy, (2) documented disease progression, (3) death, or (4) the end of study, whichever occurs first.

7.5.1. Solid Tumors and Lymphoma: CT Scan or MRI

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 recorded in the CRF. For solid tumors, the RECIST v1.1 (Eisenhauer et al 2009) will be used, and the recommended method for measuring and following tumor burden will be CT scan, to include the chest, abdomen, and pelvis. 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 consistent with RECIST v1.1.

7.5.2. Lymphoma, AML/MDS, Multiple Myeloma, MDS/MPN, and MF

For lymphoma, response assessments will be based on the Lugano Classification (Cheson et al 2014; Appendix G). For AML/MDS, MM, MDS/MPN, response assessments will be based on international uniform response criteria for the respective disease states (Cheson et al 2003 [AML; Appendix E], Cheson et al 2006 [MDS; Appendix F], Durie et al 2006 [MM; Appendix D], Savona et al 2015 [MDS/MPN, Appendix H]). Myelofibrosis response assessments will use the IWG-MRT and ELN consensus report (Tefferi et al 2013; Appendix I).

7.5.3. Lymphoma: FDG-PET or Combined PET-CT

If FDG-PET or combined PET-CT is used as a functional imaging tool for staging or response assessment of lymphoma as a part of the standard of care, the results obtained during any study phase will be captured in the CRF.

7.5.4. AML, MDS, MDS/MPN, MF, Lymphoma, and MM: Bone Marrow Examination

Bone marrow examination (aspirate and biopsy) is required at screening for Phase 1a/TGB and all Phase 1b and Phase 2 subjects with AML, MDS, MDS/MPN, MF, and MM (bone marrow examination may be omitted only with approval of the medical monitor). These subjects should have a follow-up bone marrow aspirate and biopsy performed approximately 3, 6, and 12 months after Day 1 and then every 12 months on the nearest Cycle Day 1 (± 7 days) after the first dose of treatment and as clinically indicated.

Subjects with MM only require a follow-up bone marrow examination to confirm CR, after 2 consecutive laboratory disease assessments demonstrating negative serum and/or urine immunofixation.

Lymphoma subjects in Phase 1a/TGB or Phase 1b/Cohort H with lymphoma will not require a bone marrow examination at baseline if the subject had a bone marrow examination performed after the most recent prior therapy and the results showed lymphoma involvement of the bone marrow and/or a baseline PET or PET/CT shows that the subject does have FDG-avid disease in the bone marrow. If 1 of these conditions does not apply, a baseline bone marrow biopsy is required.

Data from the pathology report result from the bone marrow examination will be captured in the CRF. All bone marrow examinations should include a unilateral aspiration and biopsy with FISH and cytogenetic testing, when feasible. 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 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.

Data from the pathology report result from the bone marrow examination will be captured in the CRF. All bone marrow examinations should include a unilateral aspiration and biopsy with FISH and cytogenetic testing, when feasible.

7.5.5. Lymphoma and AML/MDS: Immunophenotyping

For subjects with relevant hematologic malignancies (lymphoma, AML/MDS), immunophenotyping appropriate to the underlying pathology will be conducted by flow cytometry at the local laboratory at screening and Cycle 2 Day 1 and at subsequent times only as part of confirmation of CR. Results will be captured in the CRF.

7.5.6. Multiple Myeloma: Skeletal Survey

A series of x-rays will be conducted of the skull, long bones, spine, pelvis, and ribs. Skeletal surveys should be conducted at screening and then subsequently at the investigator discretion.

7.6. Performance and Quality of Life Assessments

The ECOG performance status (Table 25) must be assessed by a medically qualified individual and recorded in the CRF at the visits indicated in Table 2, Table 4, Table 6, Table 8, Table 10, Table 12, Table 14, Table 16, Table 18, Table 20, and Table 22 (as applicable to study phase and treatment cohort).

Table 25: ECOG Performance Status

Grade	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 (eg, light house work, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al 1982.

7.7. Pharmacokinetic Assessments

7.7.1. Blood Sample Collection

Pharmacokinetic plasma samples will be obtained via whole blood at the visits indicated in Table 3, Table 5, Table 7, Table 9, Table 11, Table 13, Table 15, Table 17, Table 19, Table 21, and Table 23 (as applicable to study phase and treatment cohort); collection times and windows are described in Section 7.7.1.1, Section 7.7.1.2, and Section 7.7.1.3. The exact date and time of the PK blood draws will be recorded in the CRF along with the date and time of the last dose of study drug preceding the blood draw and the time of the most recent meal. Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Subjects will receive reminder cards in advance of the study visit providing instruction to hold the dose of study drug on the day of the visit and a place to record the time of the prior dose of study drug and time of the most recent meal or snack consumed.

7.7.1.1. Pharmacokinetic Timed Instructions for Phase 1a

On Cycle 1 Days 1, 8, and 15 and on Cycle 2 Day 1 for food-effect, study subjects will refrain from taking the study drug in the morning before arriving at the research unit. Subjects should not have consumed any food within 8 hours before arriving at the research unit. A trough (predose) PK sample (30-minute window) should be drawn at each of the PK visits. Following the trough PK sample, the subject should take the assigned dose of study drug, and subsequent timed samples will be taken. Food should be withheld until 1 hour after study drug administration. If a subject mistakenly takes their morning dose at home before coming to the clinic, the PK sampling should be rescheduled at their earliest convenience.

The initial schedule for timed postdose samples (on Cycle 1 Days 1 and 15 and Cycle 2 Day 1 [food effect only]) will be as follows:

- 0.5 hour (± 5 minutes)
- 1 hour (± 10 minutes)
- 2 hours (± 15 minutes)
- 4 hours (± 15 minutes)
- 6 hours (± 30 minutes)

Adjustments to the timing of blood sampling postdose may be made based on emerging PK data; however, no more than 6 postdose timepoints will be used, and the maximum scheduled timepoint will be no greater than 6 hours postdose.

7.7.1.2. Pharmacokinetic Instructions for Phase 1a Part 2 Dose Expansion Fed Administration (Cycle 2 Day 1 Only)

On Cycle 2 Day 1, study subjects in TGA and TGB, in only the expansion cohort (Part 2), will be required to undergo PK testing after study drug administration in the fed state. If 2 expansion cohorts are enrolled in either treatment group, the food-effect study will be performed on the PAD dose level cohort. It is expected that subjects will consume 100% of the meal.

Pharmacokinetic testing conducted on Cycle 2 Day 1 will be similar to that on Cycle 1 Day 15 with respect to the timing of sample collection and evaluations. Subjects may be excused from the food-effect part of the study if they are unable to consume the meal or feel they are unable to consume the meal.

Subjects receiving INCB052793 in the fed state will have been fasted from food (not including water) overnight for at least 8 hours. A standardized high-fat, high-calorie breakfast will be given to these subjects approximately 30 minutes before administration of the study medication. Subjects must consume the entire breakfast within 30 minutes (no window after 30 minutes), and study drug will be administered 5 minutes after completing breakfast. If the subject does not complete the meal or is unable to retain the meal, there is no need to collect the PK samples. It is best to avoid antinausea medication before the meal or dose.

The high-fat, high-calorie breakfast (50% kcal from fat) will 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 prior approval of the study sponsor.

7.7.1.3. Pharmacokinetic Instructions for Phase 1b/Cohorts A Through H and Phase 2/Cohorts I and J

Subjects enrolled in Phase 1b/Cohorts B through H and Phase 2/Cohorts I and J will have PK assessments performed at the timepoints indicated in Table 3, Table 5, Table 7, Table 9, Table 11, Table 13, Table 15, Table 17, Table 19, Table 21, and Table 23. Collection of PK samples at Cycle 1 Day 1 will be performed as needed per sponsor decision based on the emerging PK data. Otherwise, coadministration will begin on Cycle 1 Day 1, and no extra samples will be collected from subjects. Sampling windows for each timepoint are as follows and are all relative to the *end* of the standard-of-care agent administration (ie, after the SC injection[s] or IV push). The timepoints below may not apply to every treatment cohort.

- T_0: predose (just before standard-of-care agent administration)
- T_{5m}: 5 minutes ± 1 minute
- $T_{0.5h}$: 30 minutes ± 5 minutes
- $T_{1.0h}$: 1 hour ± 5 minutes
- $T_{2.0h}$: 2 hours ± 10 minutes
- $T_{4.0h}$: 4 hours ± 15 minutes
- $T_{6.0h}$: 6 hours ± 30 minutes
- $T_{8.0h}$: 8 hours ± 30 minutes

7.7.2. Urine Sample Collection (Phase 1a Only)

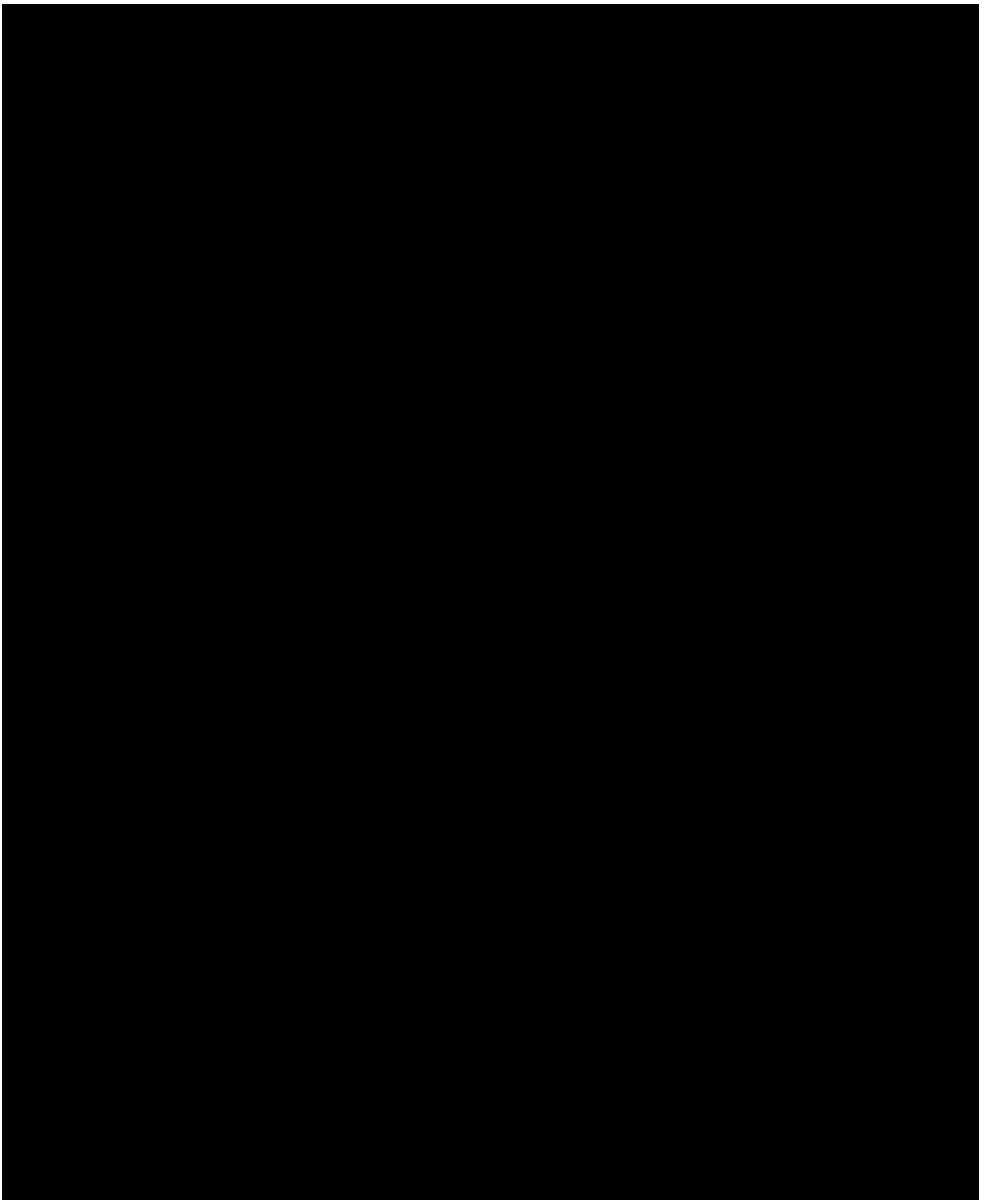
Urine will be collected from each subject at Cycle 1 Day 15 after administration of INCB052793 and a predose void. Total urine will be collected over a 6-hour interval after study drug administration. Urine containers should be kept at reduced temperature (refrigerated or ice bath) during collection. After the interval, urine should be mixed thoroughly. The total urine volume and the pH should be measured and recorded in the individual CRF. Duplicate 5 mL urine aliquots (ie, Urine Aliquot A and Urine Aliquot B) should be transferred into the prelabeled, polypropylene storage containers and frozen at or below -20°C. Shipping and handling instructions will be provided in the Laboratory Manual.

7.7.3. Bioanalytical Methodology and Analysis

The plasma samples will be analyzed for INCB052793 and INCB050465 by a validated assay. [redacted] These samples will be analyzed by Incyte Corporation (Wilmington, DE) or its designee.

Pharmacokinetic parameters will be calculated from the plasma concentrations of INCB052793 and INCB050465 according to the model-independent approach. Refer to Appendix B for a detailed list and description of the PK parameters.

[redacted]



7.9. Other Study Procedures

7.9.1. Administration of INCB052793

Subjects will self-administer INCB052793 orally with water according to a QD morning regimen as directed by the investigator. INCB052793 will be taken on an empty stomach by refraining from food consumption for 2 hours before and 1 hour after study drug administration except on days when PK [redacted] sampling is conducted, then subject will refrain from food consumption at least 8 hours before and 1 hour after study drug or as indicated in the PK section. Subjects will take study drug at the clinic after the hematology sample is drawn on clinic days when a hematology sample is obtained. Updated information will be provided if emerging PK and food-effect data suggest that an improved PK profile may be achieved by administering INCB052793 with food.

Study drug will be administered in the study clinic on days as indicated in Table 2, Table 4, Table 6, Table 8, Table 10, Table 12, Table 14, Table 16, Table 18, and Table 20.

7.9.2. Administration of INCB050465

Subjects will self-administer INCB050465 tablets orally with water, according to a QD regimen as directed by the investigator. INCB050465 will be taken on an empty stomach by refraining from food consumption for 2 hours before and 1 hour after study drug administration except on days when PK [redacted] sampling is conducted, then subject will refrain from food consumption at least 8 hours before and 1 hour after study drug or as indicated in the PK section. Updated information will be provided if emerging PK and food-effect data suggest that an improved PK profile may be achieved by administering INCB050465 with food. Study drug will be administered in the study clinic on days as indicated in Table 18.

7.9.3. Administration of Itacitinib

Subjects will self-administer itacitinib tablets orally with water, according to a QD regimen as directed by the investigator. Itacitanib will be taken without regard to food except on days when PK samples are drawn; on those days, subjects should be instructed to fast and refrain from taking itacitinib until PK samples are collected; see details in Table 22.

Study drug will be administered in the study clinic on days as indicated in Table 22.

7.9.4. Dispensing of Study Drug

An initial supply of INCB052793, INCB050465 (applicable to Cohort H only), and itacitinib (applicable to Cohort J only) will be provided to investigative sites before enrollment of the first subject. Thereafter, the site staff will contact the sponsor or its designee for resupply of INCB052793, INCB050465, and itacitinib (as applicable). When dispensing to subjects, the investigator or designee will remove the appropriate quantity of study drug from their stock, dispense the medication, and enter the amount dispensed into the CRF and drug accountability log. Full details will be provided in the Study Manual.

7.9.5. *nab*-Paclitaxel Administration

Commercial supplies of *nab*-paclitaxel will be supplied by the institution's pharmacy and administered in the clinic as either 100 mg/m^2 or 125 mg/m^2 IV over 30 minutes) on Days 1, 8, and 15 of each 28-day cycle. Refer to http://dailymed.nlm.nih.gov/dailymed/about.cfm for additional information.

7.9.6. Gemcitabine Administration

Commercial supplies of gemcitabine will be supplied by the institution's pharmacy and administered in the clinic as 1000 mg/m^2 IV (starting dose) over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Refer to http://dailymed.nlm.nih.gov/dailymed/about.cfm for additional information.

7.9.7. Dexamethasone Administration

Commercial supplies of dexamethasone will be supplied by the institution's pharmacy and administered at a starting dose of 40 mg administered orally weekly on Days 1, 8, 15, and 22 of each 28-day cycle (or Days 1, 8, 15 of each 21-day cycle if being administered with bortezomib in Phase 1b/Cohort D), without regard to food. Dexamethasone will be administered in the clinic on for all Cycle 1 doses (Days 1, 8, 15, 22) and for all subsequent doses that correspond to a scheduled visit (Days 1 and 15) for Phase 1b/Cohort B. Subjects will self-administer dexamethasone at the prescribed schedule when not visiting the clinic. Refer to http://dailymed.nlm.nih.gov/dailymed/about.cfm for additional information.

7.9.8. Carfilzomib Administration

Commercial supplies of carfilzomib will be supplied by the institution's pharmacy and administered in the clinic at a starting dose of 20 mg/m^2 IV on Days 1 and 2 followed by 27 mg/m^2 IV on Days 8, 9, 15, and 16 of Cycle 1 and for all doses of each 28-day cycle thereafter. Refer to http://dailymed.nlm.nih.gov/dailymed/about.cfm for additional information.

7.9.9. Bortezomib Administration

Commercial supplies of bortezomib will be supplied by the institution's pharmacy and administered in the clinic at a starting dose of 1.3 mg/m^2 IV or SC on Days 1, 4, 8, and 11 of each 21-day cycle. Refer to http://dailymed.nlm.nih.gov/dailymed/about.cfm for additional information.

7.9.10. Lenalidomide Administration

Commercial supplies of lenalidomide will be supplied by the institution's pharmacy and administered in the clinic on Cycle 1 Days 1, 8, and 15 as per Table 13. Subjects will self-administer lenalidomide at the prescribed schedule when not visiting the clinic. Refer to http://dailymed.nlm.nih.gov/dailymed/about.cfm for additional information.

7.9.11. Azacitidine Administration

Commercial supplies of azacitidine will be supplied by the institution's pharmacy and administered in the clinic at a starting dose of 75 mg/m^2 SC for 5 days, followed by 2 days of no

treatment, then 75 mg/m^2 for 2 days of each 28-day treatment cycle. Refer to http://dailymed.nlm.nih.gov/dailymed/about.cfm for additional information.

7.9.12. Pomalidomide Administration

Commercial supplies of pomalidomide will be supplied by the institution's pharmacy and administered in the clinic on Cycle 1 Days 1 and 15 (per Table 17). Subjects will self-administer pomalidomide at the prescribed schedule when not visiting the clinic. Dexamethasone will be coadministered at 40 mg once per day PO on Days 1, 8, 15, and 22 of each 28-day cycle. Refer to http://dailymed.nlm.nih.gov/dailymed/about.cfm for additional information.

7.9.13. Administration of Supportive Care

Supportive care, including GCSF for treatment of chemotherapy-induced neutropenia, will be supplied by the institution's pharmacy and administered according to the package insert and institutional guidelines.

7.9.14. Assessment of Compliance With Study Drug

The study subject will return all full, empty, and opened/partially used bottles of study drug at the beginning of each treatment cycle, and a compliance check (tablet count) will be performed by the clinic staff at each visit; therefore, appropriate steps should be taken to optimize compliance.

7.9.15. Distribution of Subject Reminder Cards

Subjects will be provided with subject reminder cards at each visit. The subject reminder cards will indicate the date and time of the next visit. The reminder cards will have a field for the subject to enter the date and time of the last dose taken before the visit and to record the time of the last meal when required to support the PK/[redacted] analysis. Reminder cards will inform the subject when to refrain from taking the study drug at home in the morning before the clinic visit. All necessary instructions, such as those for study drug administration, concomitant medications, and laboratory tests, should be provided to the subject in writing on this reminder card, or on accompanying written materials. After 4 treatment cycles, if the subject has been 100% compliant with study visits/requirements, subject reminder cards may be omitted at the discretion of the study staff.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions and Reporting

Treatment-emergent AEs are defined as any AE that occurs from the day a subject begins study drug.

For the purposes of this Protocol, an AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur 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).

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events page of the CRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History page of the CRF. Adverse event monitoring 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.

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

Adverse events will be assessed according to the CTCAE v4.03. The CTCAE severity Grade 5 (death) will not be used in this study; rather, information about deaths will be collected as an outcome of the event. 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.

As far as possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 4).
- Reasonable possibility that the AE is related to the study treatment: unrelated (no) or related (yes).

- Start and end dates, unless unresolved at final examination.
- Action taken with respect to study drug (eg, none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable).
- Outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- Whether it is serious, as per SAE definition provided in Section 8.3.1.

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

All AEs should be treated appropriately. If a concomitant medication or nondrug therapy is given, this action should be recorded on the AE and Prior/Concomitant medications pages of the CRF.

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 it, and the outcome.

8.2. Laboratory Test Abnormalities

8.2.1. Definitions and Reporting

Laboratory abnormalities that constitute an AE in their own right (are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug), should be recorded on the AE page of the CRF. 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, as per CTCAE, does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1, and/or per the investigator's discretion. A dose interruption or adjustment for the laboratory abnormality may be required (see Section 5.6) 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 1 of the following criteria:

- Is fatal or life-threatening (ie, immediate risk of dying).
- Results in persistent or significant disability or incapacity.
- Constitutes a congenital anomaly or birth defect.

- Is clinically meaningful (ie, defined as an event that jeopardizes the subject or requires potential medical or surgical intervention to prevent one of the outcomes listed above). Considered meaningful by the investigator as an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - Routine treatment or monitoring of the studied indication not associated with any deterioration in condition. Elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Social reasons and respite care, in the absence of any deterioration in the subject's general condition.
  - Any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, or where there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere.

8.3.2. Reporting

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has signed the ICF and up to the last study visit, or up to 30 days after the subject has stopped study treatment, whichever is later, must be reported to the sponsor (or designee) within 24 hours of learning of its occurrence. Any SAEs experienced after this period should be reported to the sponsor (or designee) only if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as the follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. Previously planned (before providing informed consent) surgeries should not be reported as SAEs unless the underlying medical condition worsens over the course of the study. When other drugs are used in combination with the study drug, the relationship to study drug can be assessed for the Incyte study drug alone, the marketed product alone (used in combination with the study drug), or as a combination of the Incyte product with the marketed product.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the sponsor or its designee. The investigator must assess if there is a reaso*nab*le possibility that the SAE is related to the study treatment: unrelated (no) or related (yes).

Serious AEs related to unblinded comparator drugs or concomitant medications/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The telephone and facsimile number of the sponsor's contact persons, specific to the study, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the CRF documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each recurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation, or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, a sponsor's associate 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, the following procedures should occur:

- The investigator must notify the sponsor or its designee immediately.
- The study drug must be discontinued immediately.
- The subject must be withdrawn from the study.
- The EOT visit evaluations must be performed.
- The investigator must complete and submit the Pregnancy Initial and Follow-Up Report forms to the sponsor or its designee.
- A serum pregnancy test must be performed to confirm the urine pregnancy test result. (The serum test should be performed at the investigative site to ensure the test will be performed promptly and the result available immediately for review.)

If a negative serum test does not confirm the urine pregnancy test result, then:

- The investigator will use his or her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine if it is in the subject's best interest to resume study drug and continue participation in the study.

To ensure subject safety, each pregnancy in a subject during maternal or paternal exposures to study drug must be reported within 24 hours of learning of its occurrence. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up to each pregnancy should be conducted 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 Study Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the sponsor's study drug of any pregnancy outcome and follow-up to the first well-baby visit. **Any SAE experienced during pregnancy must be reported on the SAE Report Form and to the sponsor or its designee.**

8.6. Warnings and Precautions

No evidence available at the time of the approval of this study Protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided 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 needed. If new, significant risks are identified, they will be added to the ICF.

8.7. Data Monitoring Committee

There will be no formal external Data Monitoring Committee for this open-label Phase 1/2 study. Approximately weekly the sponsor will conduct telephone conferences with investigators in order to review cohort-specific data and overall safety data from prior cohorts (if applicable), and to agree on dose escalation, de-escalation, and cohort expansion decisions.

8.8. Adverse Events of Special Interest

Not applicable.

8.9. 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.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint and any associated AEs via email or other written communication to the Incyte contact.

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

Efficacy/Safety Evaluable: All subjects exposed to at least 1 dose of study drug.

Pharmacokinetic/[redacted] Evaluable: Subjects who receive at least 1 dose of study drug and provide at least 1 postdose blood sample for PK/[redacted] assessments. The study pharmacokineticist will review data listings of subject dosing and sample records to identify subjects to be excluded from the analysis.

The Efficacy/Safety Evaluable population will be used for the summary of baseline, disposition, efficacy, and safety analyses. The PK/[redacted] Evaluable population will be used in the summary of all PK/[redacted] data.

9.2. Selection of Sample Size

9.2.1. Sample Size for Phase 1a and Phase 1b

The sample size was based on the adequacy of subjects (36 for Phase 1a and up to approximately 39 in Phase 1b) for dose escalation to determine the MTD and expansion evaluation. It was not based on statistical power calculations.

9.2.2. Sample Size for Phase 2

The sample size for each cohort will be guided by the Simon 2-stage design (Simon 1989), using a 1-sided Type I error of 0.10 and power of 80%. Let P0 denote a clinically uninteresting response rate (eg, for subjects with AML and high-risk MDS who failed prior therapy with HMA, P0 = 26%). In order to determine whether a target response rate (eg, 46%, which represents a 20% improvement) is likely, an initial number of subjects (eg, 9) will be treated at Stage 1. If ≤ 2 subjects have responses among these 9 subjects, it will be concluded that the true response rate is unlikely to be greater than or equal to the target rate, and no more subjects will be enrolled in that treatment group. Otherwise, if at least 3 subjects have responses among the Stage 1 subjects, 24 additional subjects will be treated in Stage 2 to estimate the response rate. At the end of Stage 2, if ≤ 11 subjects have responded among a total of 33 subjects, the study drug will be declared nonpromising. In other words, after the study is finished, if there is a sufficient number of responses in the 2 stages combined, the study drug is considered promising; otherwise it is considered nonpromising. Approximately 66 subjects will be enrolled for Cohort I and Cohort J in Phase 2.

9.3. Level of Significance

Not applicable. No formal efficacy hypotheses will be tested. All confidence intervals (CIs) will be 95%.

9.4. Statistical Analyses

9.4.1. Primary Analyses

9.4.1.1. Phase 1a and 1b

Safety analyses will be conducted for the safety evaluable population. Adverse events will be coded by the Medical Dictionary for Regulatory Activities, and incidences will be tabulated by preferred term and system organ class for all events, related events, and events of Grade 3 or higher. Quantitative safety variables and their changes from baseline (laboratory tests, vital signs, etc) will be summarized with descriptive statistics. Clinically notable abnormal values will be flagged and tabulated based on predefined criteria. The rate of DLTs will be summarized for each cohort.

9.4.1.2. Phase 2

The proportion of subjects with response by IWG response criteria for AML and IWG response criteria for MDS will be summarized.

A subject is considered a responder if the subject achieves CR, Cri, PR, or HI at any postbaseline visit. The proportion of responders will be estimated with 95% CIs; the CIs will be calculated based on the exact method for binomial distributions.

9.4.2. Secondary Analyses

The proportion of subjects with response by RECIST v1.1 criteria for solid tumors, the Lugano Classification criteria for malignant lymphoma, and the International Uniform Response Criteria for MM, IWG response criteria for AML, and IWG response criteria for MDS will be summarized. The proportion of responders will be estimated with 95% CIs; the CIs will be calculated based on the exact method for binomial distributions.

Pharmacokinetic [redacted] data will be analyzed with appropriate standard nonlinear analytic software.

9.4.2.1. Baseline Demographics and Disposition of Subjects

Descriptive statistics (eg, mean, standard deviation, range) will be derived where appropriate. Subject demographics and medical history will be summarized at baseline. The number and percentage of subjects who were enrolled and treated, who completed the study, who discontinued study drug, and who were withdrawn from the study with a primary reason for withdrawal, will be summarized for the safety population. The number of subjects enrolled by site will also be provided.

9.4.3. Other Analyses

Not applicable.

9.5. Data Monitoring Committee

Not applicable

9.6. Interim Analysis

No interim analysis is planned.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Investigational Product Description

10.1.1. Packaging, Labeling, and Preparation of INCB052793

INCB052793 tablets (5 mg or 25 mg strength) will be administered orally QD, but dose escalation can be switched to twice daily as determined by emerging PK [redacted] data. All bottles of Incyte investigational product contain the following language: "Caution: New Drug—Limited by Federal Law to Investigational Use."

10.1.2. Storage and Stability of INCB052793

INCB052793 tablets are stable for at least 2 months at ambient and accelerated storage conditions of 40°C/75% relative humidity. Stability studies are ongoing, and drug product should be stored under ambient conditions.

10.1.3. Packaging, Labeling, and Preparation of INCB050465

INCB050465 tablets are provided in high-density polyethylene bottles; no preparation is required. All bottles of Incyte investigational product contain the following language: "Caution: New Drug—Limited by Federal Law to Investigational Use."

10.1.4. Storage and Stability of INCB050465

INCB050465 drug product should be stored under ambient conditions at 15°C to 30°C (59°F to 86°F).

10.1.5. Packaging, Labeling, and Preparation of Itacitinib

Itacitinib will be provided to sites as 100 mg tablets packaged in high-density polyethylene bottles as applicable by Incyte. 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."

10.1.6. Storage and Stability of Itacitinib

Itacitinib should be stored at ambient conditions (15°C to 30°C, or 59°F to 86°F) as per the itacitinib IB.

10.2. Accountability, Handling, and Disposal of Study Drug

Responsibility for drug accountability at the study site rests with the investigator; however, the investigator may assign some of the drug accountability duties 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 will be expected to collect and retain all used, unused, and partially used containers of study drug until the end of the study. 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.

These records should include dates, quantities, batch or serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study 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 correct study drug specified.

Completed accountability records will be archived by the site. At the completion 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 site destruction of investigational supply, prior written approval must be obtained from Incyte.

11. STUDY ADMINISTRATION

11.1. Data Management

11.1.1. Data Collection

The investigator will be provided with a CRF for each subject. Entries made in the CRF must be verifiable against source documents; any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and CRF entries and will sign and date the designated pages in each subject's CRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all responses.

11.1.2. Data Management

Data management will be performed from CRFs. All CRF data will be entered into a validated database. 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.

11.2. Study Monitoring

Qualified representatives of the sponsor or its designee, "study monitors," will monitor the study according to a predetermined monitoring plan. Monitoring visits provide the sponsor with the opportunity to:

- Evaluate the progress of the study.
- Verify the accuracy and completeness of CRFs.
- Assure that all Protocol requirements, applicable laws and/or regulations, and investigator's obligations are being fulfilled.
- Resolve any inconsistencies in the study records.

The investigator must allow the study monitors to periodically review, at mutually convenient times during the study and after the study has been completed, all CRFs and office, hospital, and laboratory records supporting the participation of each subject in the study. The CRFs and other documentation supporting the study must be kept up-to-date by the investigator and the research staff at the investigative site. These study materials must be available for review by the study monitor, and/or other qualified representatives of the sponsor or its designee, at each monitoring visit.

The study monitor will review the various records of the study (CRFs, subject medical and laboratory records, and other pertinent data). The study monitor will verify the CRF data against original source documentation for accuracy and completeness. The study monitor will identify data discrepancies and collaborate with the investigator and research staff to resolve the discrepancies in a timely manner. Protocol deviations will also be identified and recorded on a "Protocol Deviation Log." The study monitor will follow an "Issue Escalation" plan in order to ensure that each issue identified during a monitoring visit is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

11.3. Protocol Adherence

The principal investigator must obtain IRB or IEC approval for the investigation. Initial IRB or IEC approval and all materials approved by the IRB or IEC for this study including the subject ICF and recruitment materials must be maintained by the investigator and made available for inspection.

Each investigator must adhere to the Protocol as described in this document and agree that changes to the Protocol, with the exception of medical emergencies, must be discussed and approved, firstly, by the sponsor or its designee and, secondly, by the IRB or IEC. Each investigator is responsible for enrolling subjects who have met the Protocol inclusion and exclusion criteria. The IRB or IEC that granted original approval, or the IRB or IEC currently responsible for overseeing the conduct of the study, must be notified of all changes in and deviations from the Protocol that may increase risk to the subject, and/or that may adversely affect the rights of the subject or validity of the investigation. The investigator must send a copy of the approval letter from the IRB or IEC to the sponsor or its designee and retain the original in the site study regulatory file.

Major eligibility deviations must be reported to the IRB or IEC in accordance with the IRB or IEC requirements. During the course of the study, the monitor must notify the sponsor or its designee of subjects found not to have met eligibility criteria. The medical monitor, in collaboration with the investigator, will determine if the subject should be withdrawn from the study.

11.4. Financial Disclosure

All clinical investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators, are required before study initiation to submit a completed Clinical Investigator Financial Disclosure Request 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 sub investigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new investigators or sub investigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Request 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 obligation to report to the sponsor or its designee any changes to the financial information previously reported. The clinical investigators will also be reminded that they must report any changes in their financial information for a period of 1 year after completion of the covered clinical study.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Sponsor Audits

At some point during the study, individuals from the sponsor's Quality Assurance department and/or their authorized representative may visit the investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the investigator's adherence to the Protocol, applicable regulations, and the sponsor's procedures, in addition to assessing the accuracy of the study data. Before initiating this audit, the investigator will be contacted by the sponsor to arrange a convenient time for this visit. The investigator and staff are expected to cooperate with the auditors and allow access to all subject records supporting the CRFs and other study-related documents.

12.2. Inspection by Regulatory Authorities

At some point during the investigational product's development program, a regulatory authority may visit the investigator to conduct an inspection of the study and the site. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the CRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

13. ETHICS

13.1. Ethical Conduct of the Study

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

13.2. Written Informed Consent

Informed consent documentation that includes both information about the study and the ICF will be prepared and given to the subject. This document will contain all elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

The principal investigator at each center will ensure that the subject is given full and adequate verbal and written information about the nature, purpose, and the possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue study drug and withdraw from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures. The principal investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject. The investigator should inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

Preparation of the ICF is the responsibility of the investigator and must include all elements required by the ICH GCP, and applicable regulatory requirements, and must adhere to the ethical principles that have their origin in the Declaration of Helsinki. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and approve all changes to site-specific ICFs. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records. Before the beginning of the study, the IRB or IEC must provide the investigator with written approval/favorable opinion of the written ICF and any other information to be provided to the subjects.

13.3. Ethics Review

It is the responsibility of the investigator to assure that all aspects of the ethics review are conducted in accordance with the Declaration of Helsinki as described in the ICH E6: Guideline for GCP, and/or local laws, whichever provides the greatest level of protection for the study participants. The Protocol and any information supplied to the subject to obtain informed consent, including written ICFs, subject recruitment procedures (eg, advertisements), and written information to be provided to subjects (information leaflets), must be reviewed and approved by a qualified IRB/IEC before enrollment of participants in the study. Before initiation of the study, the sponsor or its designee must receive documentation of the IRB or IEC approval, which specifically identifies the study/protocol, and a list of the committee members.

The principal investigator is responsible for informing the IRB or IEC of any amendment to the Protocol in accordance with local requirements. Protocol amendments and revisions to the ICF must be submitted to and approved by the IRB or IEC.

Investigators must submit progress reports to the IRB or IEC in accordance with the IRB or IEC requirements and local regulations. Annual re-approval of the study must be obtained. Copies of progress reports and annual re-approvals must be sent to the sponsor or its designee.

The principal investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The sponsor or its designee will provide this information to the principal investigator.

When the sponsor or its designee provides the investigator with a safety report, the investigator must promptly forward a copy to the IRB or IEC.

After completion or termination of the study, the investigator must submit a final report to the IRB or IEC and to the sponsor or its designee.

The investigator, as part of the records retention requirements for the study, must maintain documentation of all submissions, correspondence, and approvals to and from the IRB or IEC.

Each clinical investigator is responsible to conduct the study in accordance with the Protocol, all applicable laws, regulations, and GCP according to ICH guidelines.

13.4. Data Privacy

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.

14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

The sponsor or its designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The investigator must ensure that all records pertaining to the conduct of the clinical study (as listed above) are adequately maintained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal termination of clinical development of the investigational product.

14.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the termination of the test article for investigation. If it becomes necessary for the sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records.

The investigator must not destroy any records associated with the study without receiving approval from Incyte. 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.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable, provided it is legible and is a verified copy of the original document.

All CRF 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 CRF data and audit trail.

14.3. Confidentiality

Subject names will not be supplied to the sponsor or its designee if applicable. Only the subject number and subject's initials will be recorded in the CRF, 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.

15. 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. 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. The signed agreement is retained by the sponsor or its designee.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

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

Such methods include:

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

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

Source: CTFG 2014.

APPENDIX B. PHARMACOKINETIC ANALYTICAL PARAMETERS

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

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin® (Pharsight Corporation, Cary, NC). Additional details of analyses will be described in the data analysis plan.

APPENDIX C. CYTOCHROME P450 3A4 INHIBITORS AND INDUCERS

University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org. Accessed May 2015. Highlighted rows indicate recent additions to the lists at the time the database search was performed.

In Vivo CYP3A Inhibitors

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate AUCr > 5)						
indinavir /RIT	Protease Inhibitors	800/100 mg BID (1 day)	alfentanil	36.5	19225389	2009 Mar
tipranavir/RIT	Protease Inhibitors	500/200 mg BID (2 days)	midazolam	26.91	20147896	2010 Jun
ritonavir	Protease Inhibitors	3 doses of 100 mg over 24 h	midazolam	26.41	20002087	2009 Dec
cobicistat (GS-9350)	None	200 mg QD (14 days)	midazolam	19.03	20043009	2010 Mar
indinavir	Protease Inhibitors	800 mg TID (7 days)	vardenafil	16.25	NDA # 021400	2003 Aug
ketoconazole	Antifungals	400 mg QD (4 days)	midazolam	15.9	8181191	1994 May
troleandomycin	Antibiotics	500 mg single dose	midazolam	14.8	15536460	2004 Dec
telaprevir	Antivirals	750 mg TID (16 days)	midazolam	13.5	22162542	2012 Oct
danoprevir / RIT	Antivirals	200/100 mg QD (14 days)	midazolam	13.42	23872824	2013 Nov
elvitegravir / RIT	Treatments of AIDS	150/100 mg QD (10 days)	midazolam	12.8	NDA # 203100	2012
saquinavir / RIT	Protease Inhibitors	1000/100 mg BID (14 days)	midazolam	12.48	19792991	2009 Oct
lopinavir / RIT	Protease Inhibitors	400/100 mg BID (2 days)	alfentanil	11.47	24067429	2013 Dec
itraconazole	Antifungals	200 mg QD (4 days)	midazolam	10.8	8181191	1994 May
voriconazole	Antifungals	200 mg BID (9 days)	midazolam	9.63	21937987	2011 Nov
mibefradil	Calcium Channel Blockers	100 mg single dose	midazolam	8.86	14517191	2003 Oct
LCL161	Cancer Treatments	600 mg single dose	midazolam	8.8	23585187	2013 Jun
clarithromycin	Antibiotics	500 mg BID (7 days)	midazolam	8.39	16432272	2006 Feb
posaconazole	Antifungals	400 mg BID (7 days)	midazolam	6.23	19302901	2009 Feb
telithromycin	Antibiotics	800 mg QD (6 days)	midazolam	6.2	NDA# 021144	2004
grapefruit juice DS[2]	Food Products	240 mL TID (2 days) and 90 min, 60 min, 30 min prior to midazolam	midazolam	5.95	12953340	2003 Aug
conivaptan	Diuretics	40 mg BID (5 days)	midazolam	5.76	NDA # 021697	2005
nefazodone	Antidepressants	100-200 mg BID (12 days)	midazolam	5.44	14551182	2003 Nov
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)	midazolam	5.29	21406602	2011 Jun
saquinavir	Protease Inhibitors	1200 mg TID (5 days)	midazolam	5.18	10430107	1999 Jul
idelalisib	Kinase Inhibitors	150 mg BID (8 days)	midazolam	5.15	NDA # 206545	2014
boceprevir	Antivirals	800 mg TID (6 days)	midazolam	5.05	NDA # 202258	2011
Moderate CYP3A Inhibitors (AUCr ≥ 2 and < 5)						
erythromycin	Antibiotics	1000 mg single dose	midazolam	4.99	25139487	2014 Dec
fluconazole	Antifungals	400 mg single dose	midazolam	4.93	16172184	2005 Oct
atazanavir / RIT	Protease Inhibitors	300/100 mg BID	maraviroc	4.9	18333863	2008 Apr
darunavir	Protease Inhibitors	1200 mg BID (14 days)	saquinavir	4.9	NDA # 021976	2006
diltiazem	Calcium Channel Blockers	60 mg TID (2 days)	midazolam	4.06	21209240	2011 Nov
darunavir / RIT	Protease Inhibitors	400/100 mg BID (8 days)	sildenafil	4.0	NDA # 021976	2006
dronedarone	Antiarrhythmics	400 mg BID (14 days)	simvastatin	3.66	NDA # 022425	2009
crizotinib	Kinase Inhibitors	250 mg BID (28 days)	midazolam	3.65	NDA # 202570	2011
atazanavir	Protease Inhibitors	400 mg QD (7 days)	maraviroc	3.57	18333863	2008 Apr
aprepitant	Antiemetics	80-125 mg QD (5 days)	midazolam	3.29	12891225	2003 Aug
casopitant	Antiemetics	120 mg QD (14 days)	midazolam	3.13	20840445	2010 Oct
amprenavir	Protease Inhibitors	1200 mg BID (10 days)	rifabutin	2.93	11158747	2001 Feb
imatinib	Antineoplastic Agents	400 mg QD (7 days)	simvastatin	2.92	14612892	2003 Nov
verapamil	Calcium Channel Blockers	80 mg TID (2 days)	midazolam	2.92	8198928	1994 Mar
ledipasvir	Antivirals	30 mg QD (10 days)	simeprevir	2.69	NDA # 205123	2013
netupitant	Antiemetics	300 mg single dose	midazolam	2.44	23729226	2013 Oct
grapefruit juice	Food Products	240 mL QD (4 days)	midazolam	2.39	10546919	1999 Oct
tofisopam	Benzodiazepines	100 mg TID (9 days)	midazolam	2.36	17989974	2008 Jan
cyclosporine	Immunosuppressants	Not provided (1-5 years)	midazolam	2.21	21753749	2011 Sep
ACT-178882	Renin Inhibitors	300 mg QD (14 days)	midazolam	2.19	22849770	2013 Dec
ciprofloxacin	Antibiotics	500 mg single dose	sildenafil	2.12	16372380	2005 Dec
schisandra sphenanthera	Herbal Medications	3 capsules (= 11.25 mg deoxyschizandrin) BID (7 days)	midazolam	2.05	19552749	2009 May

cimetidine	H-2 Receptor Antagonists	200-400 mg QID (1.5 days)	midazolam	2.02	6152615	1984 Sep
FK1706	Central Nervous System Agents	60 mg QD (14 days)	midazolam	2.01	19889885	2010 Feb
lomitapide	Other Antilipemics	60 mg QD (7 days)	simvastatin	2.0	NDA # 203858	2012
		Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2)				
tabimorelin	Hormone Replacement	2.86-3.21 mg QD (7 days)	midazolam	1.93	12610745	2003 Feb
ranolazine	Cardiovascular Drugs	1000 mg BID (7 days)	simvastatin	1.89	NDA # 021526	2006
amlodipine	Calcium Channel Blockers	10 mg QD (9 days)	simvastatin	1.8	23965645	2014 Apr
lomitapide	Other Antilipemics	60 mg QD (7 days)	simvastatin	1.77	24734312	2014 Mar
fosaprepitant (IV)	Antiemetics	150 mg single 30-min infusion	midazolam	1.76	21209230	2011 Dec
Seville orange juice	Food Products	240 mL single dose	felodipine	1.76	11180034	2001 Jan
amiodarone	Antiarrhythmics	400 mg QD (4 days)	simvastatin acid	1.76	17301736	2007 May
chlorzoxazone	Muscle Relaxants	250 mg single dose (part of a 6-drug cocktail)	midazolam	1.68	11736864	2001 Nov
M100240	Antihypertensive Agents	50 mg single dose	midazolam	1.66	15051745	2004 Apr
fluvoxamine	Antidepressants	50-00 mg BID (12 days)	midazolam	1.66	14551182	2003 Nov
ranitidine	H-2 Receptor Antagonists	150 mg BID (1.5 days)	midazolam	1.66	6135440	1983 Jun
goldenseal	Herbal Medications	1,323 mg (= 24.1 mg isoquinoline alkaloids) TID (14 days)	midazolam	1.63	17495878	2008 Jan
clotrimazole	Antifungals	10 mg TID (5 days)	midazolam	1.61	20233179	2010 Feb
tacrolimus	Immunosuppressants	Not provided (1-5 years)	midazolam	1.61	21753749	2011 Sep
cilostazol	Antiplatelets	100 mg BID (7 days)	lovastatin	1.56	10702889	1999
ticagrelor	Antiplatelets	180 mg bid (7 days)	simvastatin	1.56	NDA # 022433	2011
peppermint oil	Food Products	600 mg (= 300 uL peppermint oil) single dose	felodipine	1.55	12235445	2002 Sep
ivacaftor	Cystic fibrosis treatments	150 mg BID (6 days)	midazolam	1.54	NDA # 203188	2012
GSK2248761	Transcriptase Inhibitors	100 mg QD (12 days)	midazolam	1.54	22288567	2012 Aug
roxithromycin	Antibiotics	300 mg QD (6 days)	midazolam	1.47	7995324	1994
suvorexant	Hypnotics - Sedatives	80 mg QD (14 days)	midazolam	1.47	NDA # 204569	2014
propiverine	Anticholinergics	15 mg BID (7 days)	midazolam	1.46	16183781	2005 Dec
isoniazid	Antibiotics	90 mg BID (4 days)	triazolam	1.46	6140941	1983 Dec
berberine	Herbal Medications	300 mg TID (14 days)	midazolam	1.45	21870106	2012 Feb
oral contraceptives	Oral contraceptives	OC with low doses of estrogen (< 35 ug ethinylestradiol) (> 3 months)	triazolam	1.44	6149030	1984 Nov
delavirdine	NNRTIs	400 mg TID (9 days)	indinavir	1.44	9665503	1998 Jul
daclatasvir	Antivirals	60 mg QD (7 days)	simeprevir	1.44	NDA # 205123	2013
faldaprevir	Antivirals	240 mg BID (8 days)	ethinyl estradiol	1.44	25385099	2015 Jan
simeprevir	Protease Inhibitors	150 mg QD (11 days)	midazolam	1.43	NDA # 205123	2013
atorvastatin	HMG CoA Reductase Inhibitors (Statins)	10-40 mg/day (chronic treatment)	midazolam IV	1.41	12911366	2003 Sep
tolvaptan	Vasopressin Antagonists	60 mg single dose	lovastatin	1.41	NDA # 022275	2009
almorexant	Hypnotics - Sedatives	200 mg QD (9 days)	midazolam	1.37	22990330	2013 Mar
GSK1292263	Other Antilipemics	300 mg BID (9 days)	simvastatin	1.36	23256625	2013 Jun
linagliptin	Dipeptidyl Peptidase 4 Inhibitors	10 mg QD (6 days)	simvastatin	1.34	20497745	2010 Jun
resveratrol	Food Products	1 g QD (4 weeks)	buspirone	1.33	20716633	2010 Sep
lacidipine	Calcium Channel Blockers	4 mg QD (8 days)	simvastatin	1.33	11259986	2001 Feb
cranberry juice	Food Products	240 mL double strength juice, 1 glass q 15 min x 3	midazolam	1.33	19114462	2009 Mar
pazopanib	Kinase Inhibitors	800 mg QD (17 days)	midazolam	1.32	20881954	2010 Nov
everolimus	Immunosuppressants	10 mg QD (5 days)	midazolam	1.31	23426978	2013 Apr
blueberry juice	Food Products	two doses of 300 mL, separated by 16 hours	buspirone	1.31	22943633	2013 Apr
nilotinib	Kinase Inhibitors	600 mg single dose	midazolam	1.3	NDA # 022068	2007
AMD070	Fusion Inhibitors	200 mg BID (8 days)	midazolam	1.29	18362694	2008 Apr
alprazolam	Benzodiazepines	1 mg TID (7 days)	buspirone	1.29	8300893	1993 Nov
bicalutamide	Antiandrogens	150 mg QD (>3 months)	midazolam	1.27	15509184	2004
sitaxentan	Endothelin Receptor Antagonists	100 mg QD (7 days)	sildenafil	1.27	20078609	2010 Jan
azithromycin	Antibiotics	500 mg QD (3 days)	midazolam	1.27	8720318	1996 Feb
ginkgo	Herbal Medications	120 mg TID (28 days)	midazolam	1.25	17050793	2006 Nov
teriflunomide	Other Immunomodulators	14-70 mg QD (14 days)	midazolam	1.25	NDA # 202992	2012

[1] To allow better comparability, DDI studies with the probe substrate midazolam were selected first.
When no study with midazolam was available, the AUCratio of another probe or sensitive substrate is presented.
[2] 240 mL GFJ double-strength administered TID for 3 days

In Vivo CYP3A Inducers

Inducers	Therapeutic class	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Dose (oral)	PMID or NDA #	Published
Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%))							
rifampin	Antibiotics	budesonide	99.7	36904.5	600 mg QD (7 days)	15726657	2005 Mar
mitotane	Other Antineoplastics	midazolam	94.5	Not Provided	maximum of 3.5 g TID (chronic therapy)	21220434	2011 Apr
avasimibe	Other Antilipemics	midazolam	93.5	Not Provided	750 mg/day (7 days)	12766253	2003 Sep
phenytoin	Anticonvulsants	nisoldipine	89.5	Not Provided	200-450 mg/day (chronic treatment)	8917062	1996 Nov
carbamazepine	Anticonvulsants	quetiapine	86.6	643.1	200 mg TID (26 days)	16390352	2006 Jan
enzalutamide	Antiandrogens	midazolam	85.9	Not Provided	160 mg QD (85±3 days)	NDA # 203415	2012
St John's Wort	Herbal Medications	midazolam	80.0	Not Provided	300 mg TID (14 days)	16341856	2006 Jan
rifabutin	Antibiotics	delavirdine	Not Provided	458.0	300 mg QD (14 days)	9224961	1997 Jun
phenobarbital	Anticonvulsants	verapamil	76.6	400.9	100 mg QD (21 days)	3392664	1988 Jul
Moderate Inducers (AUC decreased by 50-80% or CL increased by 2-5 fold (100-400%))							
ritonavir and St. Johns wort	None	midazolam	77.2	Not Provided	ritonavir: 300 mg BID and SJW: 300 mg TID (14 days)	19924124	2010 Feb
semagacestat	Alzheimer's Treatments	midazolam	76.4	324.6	140 mg QD (10 days)	22789530	2012 Oct
efavirenz	NNRTIs	alfentanil	76	369.4	600 mg QD (20 days)	22398970	2012 Apr
tipranavir and ritonavir	Protease Inhibitors	saquinavir	75.6	Not Provided	tipranavir: 500 mg and ritonavir: 200 mg BID (14 days)	18176328	2008 Apr
bosentan	Endothelin Receptor Antagonists	sildenafil	69.0	239.8	62.5-125 mg BID (8 weeks)	15963102	2005 Jul
genistein	Food Products	midazolam	13.7	136.9	1000 mg QD (14 days)	21943317	2012 Feb
thioridazine	Antipsychotics	quetiapine	68.7	104.5	100-300 mg QD (15 days)	22569350	2012 Jun
nafcillin	Antibiotics	nifedipine	62.6	145.1	500 mg 4 times daily (5 days)	12814453	2003 Jun
talviraline	NNRTIs	indinavir	61.7	181.2	500 mg TID (14 days)	10516944	1999 Oct
lopinavir	Protease Inhibitors	amprenavir	59.7	Not Provided	400 mg BID (4 weeks)	15060509	2004 Apr
modafinil	Psychostimulants	triazolam	57.6	35.7	200-400 mg QD (28 days)	11823757	2002 Jan
etravirine	NNRTIs	sildenafil	56.7	Not Provided	800 mg BID (13.5 days)	NDA# 022187	2008
lersivirine	NNRTIs	midazolam	51.4	105.5	1000 mg BID (14 days)	22527351	2012 Nov
Weak Inducers (AUC decreased by 20-50% or CL increased by less than 2 fold (100%))							
eslicarbazepine	Anticonvulsants	simvastatin	49.4	98.4	800 mg QD (14 days)	23726291	2013 Sep
telaprevir	Antivirals	darunavir	48.4	Not Provided	1125 mg BID (4 days)	NDA# 201917	2011
garlic	Food Products	saquinavir	44.7	Not Provided	caplet of GarliPure BID (20 days)	11740713	2002 Jan
bexarotene	Other Antineoplastics	atorvastatin	45.3	Not Provided	400 mg/m2 QD (at least two 4-week cycles)	22057855	2012 Feb
amprenavir	Protease Inhibitors	lopinavir	43.0	Not Provided	700 mg BID (2-4 weeks)	15668539	2005 Jan
raltegravir	HIV-Integrase Strand Transfer Inhibitors	darunavir	42.0	Not Provided	400 mg BID	21958880	2012 Feb
vemurafenib	Kinase Inhibitors	midazolam	39.4	Not Provided	960 mg BID (15 days)	NDA # 202429	2011
troglitazone	Thiazolidinediones	simvastatin	37.7	Not Provided	400 mg QD (24 days)	11361054	2001 May
sorafenib	Kinase Inhibitors	sirolimus	36.9	Not Provided	200 mg BID (11 days)	21045832	2010 Nov
rufinamide	Anticonvulsants	triazolam	36.7	53.4	400 mg BID (11.5 days)	NDA # 021911	2008
pleconaril	Antivirals	midazolam	34.6	52.8	400 mg TID (6 days)	16467135	2006 May
ginseng	Herbal Medications	midazolam	34.2	50.7	500 mg BID (28 days)	21646440	2012 Jun
boceprevir	Antivirals	darunavir	34.2	41.0	800 mg every 8 hrs (6 days)	23155151	2013 Mar
sulfinpyrazone	Antigout and Uricosuric Agents	cyclosporine	33.9 (change in C_{avg})		200 mg/day	11124491	2000 Dec
gingko	Herbal Medications	midazolam	33.7	52.6	120 mg BID (28 days)	18205997	2008 Feb
vinblastine	Vinca Alkaloids	midazolam IV	33.2	48.8	not provided (4 cycles)	20959500	2010 Nov
nevirapine	NNRTIs	indinavir	32.5	Not Provided	200 mg QD (14 days), then BID (19 days)	10191212	1999 May
armodafinil (R-modafinil)	Psychostimulants	midazolam	32.2	54.7	100-250 mg/day (31 days)	18076219	2008
ticagrelor	Anticoagulants and Antiplatelets	midazolam	31.7	46.5	400 mg QD (6 days)	23870610	2013 Jul
LCL161	Cancer Treatments	midazolam	29.8	34.0	600 mg single dose	23585187	2013 Jun
vicriviroc and ritonavir	Treatments of AIDS	ethinyl estradiol	29.4	Not Provided	30 mg vicriviroc and 100 mg ritonavir QD (10 days)	22015327	2011 Oct

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

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

* **Stribild** is a combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF

APPENDIX D. INTERNATIONAL UNIFORM RESPONSE CRITERIA FOR MULTIPLE MYELOMA

Response Subcategory	Response Criteria
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence[1]
CR	Negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow.
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein with urine M-protein level < 100 mg per 24 hours
PR	• ≥ 50% reduction of serum M-protein and reduction in 24 hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours • If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If serum and urine M-protein and serum FLC are unmeasurable[2], then ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%. • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD	Not meeting criteria for CR, VGPR, PR, MR or PD.
PD	Any one or more of the following: • Increase of ≥ 25% from lowest response level in: - serum M-component and /or (the absolute increase must be ≥ 0.5 g/dL) - urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h) • Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL. • Bone marrow plasma cell percentage: the absolute % must be ≥ 10% • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

[1] Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

[2] Measurable disease: serum M protein ≥1 g/dL, urine M-protein >200 mg/24 hr, or serum involved FLC levels >10 mg/dL with a normal κ/λ ratio.

All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

Source: Durie et al 2006.

APPENDIX E. 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 F. IWG RESPONSE CRITERIA FOR MYELODYSPLASTIC SYNDROME

Category	Response Criteria (responses must be at least 4 wk)
Complete remission (CR)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines Persistent dysplasia will be noted Peripheral blood: Hemoglobin ≥ 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 hemoglobin (Hgb) concentration by ≥ 2 g/dL - Transfusion dependence
Disease transformation	Transformation to AML (30% or more blasts)
Relapse after CR or PR	At least one 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
HEMATOLOGICAL 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. RESPONSE CRITERIA FOR LYMPHOMA – THE LUGANO CLASSIFICATION

Site	PET–Based Response	CT/MRI-Based Response
	Complete metabolic response:	**Complete radiologic response (all of the following):**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS[a].	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi.
Nonmeasured lesion	Not applicable.	Absent.
Organ enlargement	Not applicable.	Regress to normal.
New lesions	None.	None.
Bone marrow	No evidence of FDG-avid disease in marrow.	Normal by morphology; if indeterminate, IHC negative.
	Partial metabolic response:	**Partial remission (all of the following):**
Lymph nodes and extralymphatic sites	• Score 4 or 5[a] with reduced uptake compared with baseline and residual mass(es) of any size.	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value. • When no longer visible, 0 × 0 mm. For a node > 5 mm × 5 mm but smaller than normal, use actual measurement for calculation.
Nonmeasured lesions	Not applicable.	Absent/regressed, but no increase.
Organ enlargement	Not applicable.	Spleen must have regressed by > 50% in length beyond normal.
New lesions	None.	None.
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given for further evaluation with MRI or biopsy at interval scan.	Not applicable.
	No metabolic response:	**Stable disease:**
Target nodes/nodal masses, extranodal lesions	Score of 4 or 5[a] with no significant change in FDG uptake from baseline at interim or EOT.	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
Nonmeasured lesions	Not applicable.	No increase consistent with progression.
Organ enlargement	Not applicable.	No increase consistent with progression.
New lesions	None.	None.
Bone marrow	No change from baseline.	Not applicable.

Site	PET-CT–Based Response	CT-Based Response
	Progressive metabolic disease:	**Progressive disease (requires at least one of the following):**
Individual target nodes/nodal lesions	Individual target nodes/nodal lesions: • Score 4 or 5[a] with an increase in intensity of uptake from baseline and/or • New FDG-avid foci consistent with lymphoma at interim or EOT assessment. Extranodal lesions: • New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment. New lesions: • New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered. Bone marrow: • New or recurrent FDG-avid foci.	PPD progression: • An individual node/lesion must be abnormal with all of the following: ○ LDi > 1.5 cm ○ Increase by ≥ 50% from PPD nadir ○ An increase in LDi or SDi from nadir ▪ 0.5 cm for lesions ≤ 2 cm ▪ 1.0 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. • New or recurrent splenomegaly. • New or clear progression of preexisting nonmeasured lesions. • Regrowth of any previously resolved lesions. • A new node > 1.5 cm in any axis. • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. • Assessable disease of any size unequivocally attributable to lymphoma. • New or recurrent involvement of the bone marrow.

Source: Cheson et al 2014.

APPENDIX H. INTERNATIONAL CONSORTIUM PROPOSAL OF UNIFORM RESPONSE CRITERIA FOR MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS (MDS/MPN) IN ADULTS

Response Subcategory	Response Criteria
CR	Presence of all of the following improvements: • Bone marrow: ≤ 5% myeloblasts (including monocytic blast equivalent in case of CMML) with normal maturation of all cell lines and return to normal cellularity.[a] • Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤ Grade 1 fibrosis).[b] • Peripheral blood:[c] - WBC ≤ 10×10^9 cells/L. - Hgb ≥ 11 g/dL. - Platelets ≥ 100×10^9/L; ≤ 450×10^9/L. - Neutrophils ≥ 1.0×10^9/L. - Blasts 0%. - Neutrophil precursors reduced to ≤ 2%. - Monocytes ≤ 1×10^9/L. • Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly. Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia.[a]
Complete Cytogenetic Remission	Resolution of previously present chromosomal abnormality (known to be associated with myelodysplastic, syndrome myeloproliferative neoplasms, or MDS/MPN), as seen on classic karyotyping with minimal of 20 metaphases or FISH.[d]
PR	Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining > 5% of cellularity except in cases of MDS/MPN with ≤ 5% bone marrow blasts at baseline.
Marrow Response	• Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above. • Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining > 5% of cellularity, or reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 months apart.

Response Subcategory	Response Criteria
Clinical Benefit	Requires 1 of the following in the absence of progression or CR/partial response and independent of marrow response (cord blood response must be verified at ≥ 8 week) to be considered a clinical benefit: Erythroid response: • Hgb increase by ≥ 2.0 g/dL. • Transfusion independence (TI) for > 8 week for patients requiring at least 4 packed red blood cell transfusions in the previous 8 weeks. • Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤ 8.5 g/dL will count in the red blood cell TI response evaluation.[e] Platelet response: • Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 weeks. • Pretreatment ≤ 20×10^9/L: increase from < 20×10^9/L to >20×10^9/L and by ≤ 100%. • Pretreatment > 20×10^9/L but ≤ 100×10^9/L: absolute increase of ≥ 30×10^9/L.[e] Neutrophil response: • Pretreatment ≤ 0.5×10^9/L: at least 100% increase and an absolute increase ≥ 0.5×10^9/L. • Pretreatment > 0.5×10^9/L and ≤ 1.0×10^9/L: at least 50% increase and an absolute increase ≥ 0.5×10^9/L.[e] Spleen response: • Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable becomes not palpable.
Progressive Disease	Combination of 2 major criteria, 1 major and 2 minor criteria, or 3 minor criteria from list: **Major criteria:** Increase in blast count:[f] • < 5% blasts: ≥ 50% increase and to > 5% blasts. • 5%-10% blasts: ≥ 50% increase and to > 10% blasts. • 10%-20% blasts: ≥ 50% increase and to > 20% blasts. • 20%-30% blasts: ≥50% increase and to > 30% blasts.[g] Evidence of cytogenetic evolution:[h] • Appearance of a previously present or new cytogenetic abnormality in complete cytogenetic remission via FISH or classic karyotyping. • Increase in cytogenetic burden of disease by ≥ 50% in partial cytogenetic remission via FISH or classic karyotyping. New extramedullary disease: • Worsening splenomegaly: - Progressive splenomegaly that is defined by IWG-MRT: the appearance of a previously absent splenomegaly that is palpable at > 5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of > 10 cm. • Extramedullary disease outside of the spleen.

Response Subcategory	Response Criteria
	Minor criteria: • Transfusion dependence.[i] • Significant loss of maximal response on cytopenias ≥ 50% decrement from maximum remission/response in granulocytes or platelets. • Reduction in Hgb by ≥1.5g/dL from best response or from baseline as noted on complete blood count. Evidence of clonal evolution (molecular).[j]

CMML = chronic myelomonocytic leukemia; CR = complete remission; FISH = fluorescence *in situ* hybridization; IWG-MRT = International Working Group for Myelofibrosis Research and Treatment; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasm; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; PR = partial remission; TI = transfusion independence; TSS = Total Symptom Score; WBC = white blood cell.

[a] Presence of dysplastic changes, which may be interpreted within the scope of normal range of dysplastic changes, may still exist in the presence of CR as allowed in MDS IWG. Marrow should exhibit age-adjusted normocellularity in CR.

[b] If there is no significant fibrosis present on the initial bone marrow biopsy, a second biopsy is not required to prove resolution of fibrosis. Grading of fibrosis in measurement of treatment response should be according to the European Consensus System.

[c] Given the current lack of a validated tool to assess complete resolution of symptoms in MDS/MPN, "CR with resolution of symptoms" (a complete resolution of disease-related symptoms as noted by the MPN-SAF TSS in presence of CR) will be a provisional category of disease response.

[d] Loss of cytogenetic burden of disease by (via FISH or classic karyotyping) known to adversely affect prognosis is required to reach complete cytogenetic remission. Decrease in the cytogenetic burden of disease must be by ≥ 50% (via FISH or classic karyotyping) to be indicative of a partial cytogenetic response. Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on the performance characteristics of the specific probes used.

[e] Resolution of abnormal peripheral blood counts must persist for at least 2 separate analyses over at least 8 weeks. In the case of proliferative MDS/MPN, CR will include resolution of thrombocytosis to a normal platelet count (150-450 × 10^9/L) and resolution of leukocytosis to WBC ≤ 10 × 10^9 cells/L but ≥ 1.5 × 10^9/L. Hemoglobin should be maintained > 11 g/dL and platelets ≥100 × 10^9/L without the support of transfusions. Clinical benefit may occur when these changes occur in absence of other changes required for CR or marrow response. Platelet and packed red blood cell TI would be considered for clinical benefit, and duration of TI should be monitored. Reduction in myeloid precursors (promyelocytes, myelocytes, metamyelocytes, nucleated red blood cells) to less than appreciable levels (≤ 2%-3%) and/or 1 × 10^9/L monocytosis in the absence of infection, cytokine treatment, or other reactive causes.

[f] Blasts as measured from the bone marrow.

[g] Patients with development of acute myeloid leukemia from MDS/MPN; 20%-30% blasts may be allowed on some clinical trials for patients with MDS/MPN.

[h] Increase in cytogenetic burden of disease by ≥ 50% (via FISH or classic karyotyping). Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on specific probes used.

[i] Transfusion dependency is defined by a history of at least 2 U of red blood cell transfusions in the past month for a hemoglobin level < 8.5 g/dL that was not associated with clinically overt bleeding. Cytopenias resulting from therapy should not be considered in assessment of progression.

[j] The identification of new abnormalities using single nucleotide polymorphism arrays or sequencing or a clearly significant increase in mutational burden of a previously detected abnormality. Precise criteria for defining new abnormalities and what exactly constitutes a significant increase in mutational burden are open to interpretation; this criterion should be used conservatively based on current evidence.

Source: Savona et al 2015.

APPENDIX I. REVISED RESPONSE CRITERIA FOR MYELOFIBROSIS: IWG-MRT AND ELN CONSENSUS REPORT

Response Category	Required Criteria (for All Categories, Benefit Must Last for ≥ 12 Weeks to Qualify as a Response)
CR	• Bone marrow:[a] Age-adjusted normocellularity; < 5% blasts; ≤ Grade 1 MF.[b] • 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.[c] • Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH.
PR	• 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.[d] • Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH. • Bone marrow:a Age-adjusted normocellularity; < 5% blasts; ≤ Grade 1 MF[e], 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.[f] • Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH.
CI	• The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia.[g]
Anemia response	• Transfusion-independent patients: a ≥ 20 g/L increase in hemoglobin level.[h] • Transfusion-dependent patients: becoming transfusion-independent.[i]
Spleen response	• Baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable[j] or • Baseline splenomegaly that is palpable at > 10 cm, below the LCM, decreases by ≥ 50%.[j] - 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[k]	• 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.

CI = clinical improvement; CR = complete remission; CT = computed tomography; EMH = extramedullary hematopoiesis; LCM = left costal margin; MF = myelofibrosis; MRI = magnetic resonance imaging; PR = partial remission; PRBC = packed red blood cells; UNL = upper normal limit.

[a] Baseline and post-treatment bone marrow slides are to be interpreted at 1 sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.

[b] Grading of MF is according to the European classification.
[c] Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, < 5% immature myeloid cells is allowed.
[d] Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, < 5% immature myeloid cells is allowed.
[e] Grading of MF is according to the European classification.
[f] Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, < 5% immature myeloid cells is allowed.
[g] 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 CTCAE version 4.0. In addition, assignment to CI requires a minimum platelet count of $\geq 25{,}000 \times 10^9$/L and absolute neutrophil count of $\geq 0.5 \times 10^9$/L.
[h] 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.
[i] Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of PRBC, in the 12 weeks prior to 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 prior to 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.
[j] 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.
[k] Progressive disease assignment for splenomegaly requires confirmation by MRI or CT 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.

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