Official Title: A Phase 1/2, Open-Label, Dose-Escalation/Dose-Expansion, Safety and Tolerability Study of INCB057643 in Subjects With Advanced Malignancies

NCT Number: NCT02711137

Document Date: Clinical Study Protocol: 22 OCT 2018

Clinical Study Protocol

INCB 57643-101 / NCT02711137

A Phase 1/2, Open-Label, Dose-Escalation/Dose-Expansion, Safety and Tolerability Study of INCB057643 in Subjects With Advanced Malignancies

Product:	**INCB057643**
IND Number:	**128,688**
EudraCT Number	**2017-002641-29**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Original Protocol (Version 0):	**17 DEC 2015**
Amendment (Version) 1:	**18 JAN 2016**
Amendment (Version) 2:	**08 JUL 2016**
Amendment (Version) 3:	**14 MAR 2017**
Amendment (Version) 4:	**07 JUN 2017**
Amendment (Version) 5:	**11 OCT 2017**
Amendment (Version) 6:	**06 MAY 2018**
Amendment (Version) 7:	**22 OCT 2018**

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

INVESTIGATOR'S AGREEMENT

I have read INCB 57643-101 Protocol Amendment 7 (Version 7 dated 22 OCT 2018) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: INCB057643	
Title of Study: A Phase 1/2, Open-Label, Dose-Escalation/Dose-Expansion, Safety and Tolerability Study of INCB057643 in Subjects With Advanced Malignancies	
Protocol Number: INCB 57643-101	**Study Phase:** 1/2
Indication: Advanced Malignancies	

Primary Objective:

- To assess the safety and tolerability of INCB057643 as monotherapy and in combination with standard of care (SOC) agents in subjects with advanced malignancies.

Secondary Objectives:

- To evaluate the pharmacokinetics (PK) of INCB057643 when administered as monotherapy in the fasted state and in the fed state (food effect; Part 2 only) and when administered in combination with SOC agents in the fasted state.
- To assess the pharmacodynamics (PD) of INCB057643 when administered as monotherapy in subjects with advanced malignancies.
- To evaluate preliminary efficacy of INCB057643 when administered as monotherapy and in combination with SOC agents based on the investigator assessment of response using criteria appropriate for each disease in subjects with advanced malignancies.

[redacted]

Primary Endpoint:

- Safety and tolerability of INCB057643 as monotherapy and in combination with SOC agents as assessed by clinical laboratory assessments, physical examinations, 12-lead electrocardiograms (ECGs), and adverse events (AEs).

Secondary Endpoints:

- C_{max}, T_{max}, C_{min}, AUC_{0-t}, and $AUC_{0-\tau}$ of INCB057643 at Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 2 Day 1 (food effect; Part 2 only).
- Pharmacodynamic profile of INCB057643 using a plasma PD assay.
- Objective response rate (ORR) in subjects with measurable or evaluable diseases as determined by the investigator assessment of response using the criteria appropriate for each disease.

[redacted]

Overall Study Design:

This is an open-label, dose-escalation/dose-expansion study of the bromodomain and extra-terminal (BET) inhibitor INCB057643 as monotherapy or in combination with SOC agents in subjects with advanced malignancies. Subjects will receive INCB057643 continuously administered orally in 21- or 28-day cycles, as applicable to regimen schedules in combination. Alternative administration schedules may be assessed if indicated by emerging safety, PK, or PD data. The study consists of 4 parts. Parts 1 and 2 will evaluate INCB057643 as monotherapy, and Parts 3 and 4 will evaluate INCB057643 in combination with SOC agents.

Part 1, Monotherapy Dose Escalation, will determine the maximum tolerated dose (MTD) of INCB057643 and/or a tolerated dose that reaches the desired target inhibition (ie, a pharmacologically active dose [PAD]; plasma concentration exceeding *ex vivo* or projected c-Myc IC_{50} for approximately 6-12 hours or achieves clinical response). Part 1 will be conducted in 3 disease-specific treatment groups.

Part 2, Monotherapy Dose Expansion, will further evaluate the safety, preliminary efficacy, PK, and PD of the treatment group–specific dose selected in Part 1 (at ≤ the MTD) in select tumor types postulated to be particularly susceptible to inhibition of BET proteins.

Part 3, Combination Dose-Escalation (C-ES), will determine the MTD and/or a tolerated dose (the recommended phase 2 dose [RP2D]) of the combination of INCB057643 with one of the SOC agents. Part 3 will be conducted in 6 disease-specific treatment groups.

Part 4, Combination Dose-Expansion (C-EX), after identification of the RP2D in combination regimens in Part 3, will further determine safety, tolerability, efficacy, PK, and PD. Part 4 will be conducted in 4 treatment groups. The sponsor may decide not to expand any or some cohorts.

As of MAR 2018, no further subjects are being enrolled in all the cohorts due to a less favorable benefit/risk assessment based on emerging data, mainly the histopathological finding of cardiac myopathy observed in the preclinical 3-month toxicology study in monkeys.

Part 1 – Monotherapy Dose Escalation

The study began with dose escalation in Part 1, which comprises 3 disease-specific treatment groups. Each treatment group will use a 3 + 3 design to determine the tolerated dose over a 21-day cycle.

Part 1 will be conducted in 3 disease-specific treatment groups, as follows:

- Treatment Group A (TGA) will include subjects with any advanced solid tumor or lymphoma.
- Treatment Group B (TGB) will include subjects with any acute leukemia or high-risk myelodysplastic syndrome (HR-MDS), myelodysplastic syndrome (MDS)/myeloproliferative neoplasm (MPN), or MF.
- Treatment Group C (TGC) will include subjects with multiple myeloma (MM).

Enrollment into the study began in TGA. The initial dose level was 8 mg once daily (QD). Once a PAD has been identified in TGA, TGB and TGC will begin parallel enrollment at that PAD. Subsequently, dose escalation will proceed independently in the 3 treatment groups to an MTD (or a tolerated PAD if an MTD is not reached), each using a 3 + 3 design. If there is a distinct discrepancy in tolerability among different disease types within the same treatment group, additional disease-specific dose-escalation schedules may be initiated.

Each dose-escalation cohort will initially enroll at least 3 subjects. If no dose-limiting toxicities (DLTs) are observed in the initial 3 subjects, another cohort will begin enrollment at the next highest dose level. Dose escalations between cohorts may be up to 100% until a DLT is observed, after which dose escalations in the relevant treatment group will be limited to no more than 50% above the previous level.

If 1 DLT is observed in the first 3 subjects, at least 3 additional subjects will be enrolled in that cohort. If a DLT occurs in one-third or more of the total cohort (ie, ≥ 2 of 6 subjects), then the MTD will be deemed to have been exceeded, and the next lower dose level will be deemed to be the tolerated dose. Thus, the MTD will be defined as 1 dose level below the nontolerated dose (NTD) at which one-third or more of subjects in a particular cohort report DLTs. If the first cohort exceeds the MTD, a dose de-escalation will

be considered.

The sponsor, in consultation with participating investigators, may elect to investigate 1 or more dose levels less than the NTD or expand a dose cohort(s) deemed tolerable to up to 12 subjects in order to obtain additional PK, PD, and safety data before determining the MTD.

Individual subjects within each cohort will undergo reductions/interruptions in INCB057643 administration according to prescribed safety parameters. Subjects tolerating INCB057643 at the assigned dose for at least 4 cycles may be considered for a dose increase if a higher dose has been found to be tolerated in a subsequent cohort. Dose escalations will be accomplished using the following options: 1) increasing the number of tablets taken at each QD administration, or 2) increasing administration frequency to twice daily (BID), or 3) increasing the number of tablets taken at 1 or more dose administrations and increasing the frequency to BID. Subjects will continue to receive INCB057643 in 21-day cycles until withdrawal criteria are met (eg, toxicity, disease progression).

Part 2 – Monotherapy Dose Expansion

Part 2 of the study will evaluate the treatment group–specific dose selected in Part 1 in specific tumor types postulated to be particularly susceptible to inhibition of BET proteins. A dose up to the MTD may be selected for use in each expansion cohort by the sponsor and investigators. More than 1 dose of INCB057643 and/or schedule may be assessed pending emerging safety, PK, and PD data. Part 2/TGA will enroll up to approximately 165 subjects with specified solid tumors or lymphoma. The high-grade serous ovarian cancer cohort will include approximately 20 subjects. At least 5 of these subjects will have BRD4 amplification, and at least another 5 will have MYC amplification/ overexpression/translocation. The BRD4 and MYC molecular signature will be identified for enrollment eligibility by known status before subject consenting. The mCRPC cohort will include approximately 20 subjects. At least 5 of these subjects will have androgen receptor splice variant 7 (AR-V7) identified for enrollment eligibility by known status before subject consenting, and another 5 will have poorly differentiated neuroendocrine phenotype identified by local investigators and pathologists before subjects sign the informed consent form (ICF). A non-Hodgkin's lymphoma (NHL) cohort will include approximately 45 subjects, 5 to 15 of those having a diagnosis of "double-hit" or "triple-hit" (overexpression and/or translocation of MYC and BCL2 and/or BCL6) diffuse large B-cell lymphoma (DLBCL), 5 to 15 of those having a diagnosis of follicular lymphoma, and 5 to 15 of those to enroll other NHLs such as DLBCL, Burkitt's lymphoma, or B-cell lymphoma, unclassifiable (with features intermediate between DLBCL and Burkitt's lymphoma). The other disease-specific and molecularly defined groups in TGA (pancreatic adenocarcinoma, breast cancer, glioblastoma multiforme, and Ewing's sarcoma) will enroll approximately 5 to 15 subjects each. Efforts should be made to identify subjects with a pathway alteration relevant to BET signaling such as MYC or BRD amplification in these tumor types. An additional group of up to approximately 20 subjects with any other tumor (except those specified previously) known to have pathway alteration relevant to BET protein signaling will also be enrolled with medical monitor approval. Part 2/TGB will enroll approximately 45 subjects (5 to 15 in each tumor type) with acute myeloid leukemia (AML), HR-MDS, MDS/MPN, and MF. Part 2/TGC will enroll approximately 5 to 15 subjects with MM.

If $\geq$ 33% of subjects in a Part 2 expansion cohort experience DLTs during Cycle 1, then further enrollment to the cohort will be stopped, and a lower dose level may be explored.

During dose escalation and expansion, the small number of subjects in each group and heterogeneity of dose and subject characteristics within the groups is the reason for not having predefined efficacy stopping criteria.

Individual dose titration will be permitted according to Protocol-defined safety parameters. Subjects will continue to receive INCB057643 in 21-day cycles until withdrawal criteria are met (eg, toxicity, disease progression). Additional PK assessments for food effect on drug exposure will be performed in the first 12 subjects enrolled into Part 2/TGA. Additional subjects may be enrolled if there are data quality issues

among the initial 12 subjects.

Part 3 – Combination Dose Escalation (C-ES)

Part 3 will determine the MTD and/or a tolerated dose of the combination (the RP2D) of the combination of INCB057643 and one of the SOC agents in relapsed or refractory advanced or metastatic solid tumor and hematologic malignancies. The starting dose of INCB057643 in the combination treatment groups will be the PAD or 1 dose level below the MTD of INCB057643 monotherapy identified in Part 1 of this study. Pending emerging data in Part 1 and Part 2, a lower starting dose of INCB057643 could be selected for all or several combinations in Part 3 (eg, 2 dose levels below the MTD of INCB057643 in Part 1). Starting doses of the SOC combination agents will be selected from conventional dose regimens for the first dose cohort and can be modified for the subsequent cohorts, pending emerging safety data,. INCB057643 doses will not exceed the monotherapy MTD to be identified in Part 1.

Combination treatment groups will escalate independently and in parallel until the MTD and/or a tolerated dose (the RP2D) of the combinations is identified and will be followed by independent expansion cohorts at the selected dose(s) in Part 4. Pending emerging data, more than 1 RP2D dose could be explored in each expansion cohort in Part 4.

Dose escalation will follow the 3 + 3 design. The sponsor, in consultation with participating investigators, may elect to expand a dose cohort(s) deemed tolerable to up to 12 subjects in order to obtain supplemental PK, PD, and safety.

Part 3 will be conducted in 6 disease-specific treatment groups, as follows:

- C-ES-TGA (INCB057643 in combination with gemcitabine): any solid tumor for which treatment with gemcitabine is relevant.
- C-ES-TGB (INCB057643 in combination with paclitaxel): any solid tumor for which treatment with paclitaxel is relevant.
- C-ES-TGC (INCB057643 in combination rucaparib; conducted in the United States only): any solid tumor for which treatment with rucaparib is relevant.
- C-ES-TGD (INCB057643 in combination with abiraterone): any mCRPC subjects eligible to receive abiraterone plus prednisone.
- C-ES-TGE (INCB057643 in combination with ruxolitinib; conducted in the United States only): any MF subjects currently receiving ruxolitinib with an inadequate response.
- C-ES-TGF (INCB057643 in combination with azacitidine): any AML and HR-MDS subjects eligible to receive azacitidine.

Part 4 – Combination Dose Expansion (C-EX)

After identification of the RP2D in combination regimens in Part 3, Part 4 will enroll subjects with relapsed or refractory advanced or metastatic solid tumor and hematologic malignancies to further determine safety, tolerability, efficacy, PK, and PD in 4 disease-specific treatment groups. The sponsor may decide not to expand any or some cohorts pending emerging data.

Part 4 will be conducted in 4 disease-specific treatment groups, as follows:

- C-EX-TGA (INCB057643 in combination rucaparib; conducted in the United States only): any *BRCA* wild type platinum-resistant mHGSOC (epithelial ovarian/fallopian tube/primary peritoneal cancer) subjects eligible to receive rucaparib.
- C-EX-TGB (INCB057643 in combination with abiraterone): any mCRPC subjects who have progressed on first-line enzalutamide for metastatic disease and who are eligible to receive abiraterone plus prednisone (chemotherapy treatment naive); OR any mCRPC subjects who have demonstrated prostate-specific antigen (PSA) progression with or without radiologic progression while being treated with abiraterone plus prednisone and who are clinically stable and will remain on abiraterone plus

prednisone (prior chemotherapy is allowed).

- C-EX-TGC (INCB057643 in combination with ruxolitinib; conducted in the United States only): any MF subjects currently receiving ruxolitinib with an inadequate response.
- C-EX-TGD (INCB057643 in combination with azacitidine): any AML and HR-MDS subjects eligible to receive azacitidine.

Study Population:

Subjects with relapsed or refractory advanced or metastatic malignancies as noted below.

Key Inclusion Criteria:

- Men and women aged 18 years or older.
- Histologically or cytologically confirmed diagnosis of advanced malignancy:

Part 1 – Monotherapy Dose Escalation:

- TGA: Advanced solid tumor or lymphoma
- TGB: Acute leukemia (any), HR-MDS, MDS/MPN, or MF
- TGC: MM

Part 2 – Monotherapy Dose Expansion:

- TGA:
  - Pancreatic adenocarcinoma
  - mCRPC
  - Breast cancer
  - High-grade serous ovarian cancer
  - Glioblastoma multiforme
  - NHL
  - Ewing's sarcoma
  - Any solid tumor or lymphoma (except specified above) with any pathway alteration relevant to BET protein signaling, [redacted], which is hypothesized to be susceptible to INCB057643 monotherapy (require approval by medical monitor).
- TGB: AML, HR-MDS, MDS/MPN, or MF
- TGC: Measureable/evaluable MM, defined as one or more of the following:
  - Serum M-protein ≥ 0.5 g/dL
  - Urine M-protein ≥ 200 mg/24 h
  - Serum free light chain (FLC): Involved FLC level ≥ 10 mg/dL provided serum FLC ratio is abnormal

Part 3 – Combination Dose Escalation (C-ES):

- C-ES-TGA: any solid tumor for which treatment with gemcitabine is relevant.
- C-ES-TGB: any solid tumor for which treatment with paclitaxel is relevant.
- C-ES-TGC (conducted in the United States only): any solid tumor for which treatment with rucaparib is relevant.
- C-ES-TGD: any mCRPC subjects eligible to receive abiraterone plus prednisone.
- C-ES-TGE (conducted in the United States only): any MF subjects currently receiving ruxolitinib with an inadequate response.
- C-ES-TGF: any AML and HR-MDS subjects eligible to receive azacitidine.

Part 4 Combination Dose Expansion (C-EX):

- C-EX-TGA (conducted in the United States only): any *BRCA* wild type platinum-resistant mHGSOC (epithelial ovarian/fallopian tube/primary peritoneal cancer) subjects eligible to receive rucaparib.
  - Platinum-resistant disease is defined by disease progression within 6 months of completing platinum-based therapy.
  - Known *BRCA* wild type by a validated assay before consenting.
  - Subjects must be poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor naive or have had a clinical response (complete response or partial response) to a prior PARP inhibitor and progressed and have a *BRCA* status that was shown to be *BRCA* wild type at the time of consent.
- C-EX-TGB: any mCRPC subjects who have progressed on first-line enzalutamide for metastatic disease and who are eligible to receive abiraterone plus prednisone (chemotherapy treatment naive); OR any mCRPC who have demonstrated PSA progression with or without radiologic progression while being treated with abiraterone plus prednisone and who are clinically stable and will remain on abiraterone plus prednisone (prior chemotherapy is allowed).
  - Progression is defined by the Prostate Cancer Working Group 3 (PCWG3) Guidelines (blood-based PSA or imaging [nodes, viscera, and bone] at study entry).
  - mCRPC subjects must maintain a castrate level of testosterone documented (< 50 ng/dL) during the screening period and while on study.
- C-EX-TGC (conducted in the United States only): any MF subjects currently receiving ruxolitinib with an inadequate response, as defined below:
  - Palpable spleen of > 10 cm below the left subcostal margin on physical examination at screening OR
  - Palpable splenomegaly of 5 to 10 cm below left subcostal margin on physical examination AND active symptoms of MF at screening as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form.
  - MF subjects must be receiving ruxolitinib for ≥ 6 months with a stable dose for ≥ 8 weeks (acceptable doses are 5 to 25 mg BID).
- C-EX-TGD: any AML and HR-MDS subjects eligible to receive azacitidine.
  - 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
    - % increase in bone marrow blasts
    - Relapsed disease after response
    - At least 4 cycles of treatment without clinical benefit (hematological improvement or better)

- Prior therapy, as follows:
  - For Parts 1 and 2/TGA and TGB, subjects must have progressed following at least 1 line of prior therapy, and there is no further established therapy that is known to provide clinical benefit (including subjects who are intolerant to, not eligible for, or refuse the established therapy).
    - Subjects with AML are eligible if they have relapsed and/or refractory disease, if they are ≥ 65 years of age and are not candidates for or have refused standard chemotherapy, or if they have no established standard of care that is known to provide clinical benefit in the judgement of the investigator.
    - Subjects with MF must be resistant, refractory, or intolerant to ruxolitinib therapy.

- For Parts 1 and 2/TGC, MM subjects must have relapsed from or have been refractory to ≥ 2 prior treatment regimens, including a proteasome inhibitor and an immunomodulatory drug, and have no current standard options available.
- For Parts 3 and 4, subjects must have progressed following at least 1 line of prior therapy, and the treatment with the select SOC is relevant for the specific disease cohort.

- For subjects with solid tumors and lymphoma in all parts of the study (where applicable), willingness to undergo a pretreatment core or excisional tumor biopsy (except for glioblastoma) or availability of a tumor block or 25 unstained slides from biopsy or resection of primary tumor or metastasis that is preferably ≤ 1 year old and obtained after completion of last treatment. For subjects with hematologic malignancies in which bone marrow biopsy and/or aspirate is part of the disease assessment, willingness to undergo a pretreatment bone marrow biopsy and/or aspirate (as appropriate to disease). If a biopsy is not possible or contraindicated, or the tissue requirement cannot be satisfied, this may be omitted with approval from the medical monitor. In all cases, preferably, biopsies will be confirmed to contain adequate tumor tissue by a local pathology review.
- Life expectancy > 12 weeks; for MF subjects in Parts 3 and 4, life expectancy > 24 weeks.
- ECOG performance status score:
  - Parts 1 and 3: 0 or 1
  - Parts 2 and 4: 0, 1, or 2
- Willingness to avoid pregnancy or fathering children based on the criteria below:
  - Women of childbearing potential must have a negative serum pregnancy test at screening and immediately before the first dose (within 24 hours) of study drug.
  - Women of nonchildbearing potential are defined as surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 24 months of amenorrhea and at least 50 years of age.
  - Men and women of childbearing potential must agree to take appropriate precautions (ie, use at least 2 forms of contraception) to avoid pregnancy or fathering children from screening through follow-up (at least 28 days after the last dose of all study medications). Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subjects and their understanding confirmed.
- Females must agree to abstain from breastfeeding during study participation and for 28 days after study drug discontinuation.
- Males must also agree to refrain from donating semen or sperm during treatment and for 28 days after discontinuation from this study.
- Ability to comprehend and willingness to sign an ICF.

Key Exclusion Criteria:

- Inadequate bone marrow function demonstrated by any of the following:

Laboratory Parameter	Part 1/ TGA	Part 2/ TGA	Parts 1 and 2/ TGC[a]	Part 3-C-ES/TGA/ TGB/TGC/TGD and Part 4/C-EX-TGA/TGB	Part 3/C-ES-TGE and Part 4/C-EX-TGC
Hemoglobin (g/dL)	< 10.0	< 8.0	< 8.0	< 9.0	Subjects unwilling to receive red blood cell transfusion to treat low hemoglobin levels are excluded.
Platelet count ($\times 10^9$/L)	< 100	< 100	< 75	< 100	< 50 in 4 weeks before screening or platelet transfusions within 8 weeks of screening.
Absolute neutrophil count ($\times 10^9$/L)	< 1.5	< 1.0	< 1.0	< 1.5	< 0.5 in the 4 weeks before screening.

Note: No specific hematologic exclusion criteria apply for subject with AML/HR-MDS in Parts 1 and 2/TGB, Part 3 C-ES-TGF or Part 4 C-EX-TGD. The medical monitor will review all complete blood count parameters before approving enrollment into the study.

[a] Multiple myeloma subjects in Part 2 only: < 50×10^9/L if 50% of bone marrow nucleated cells are plasma cells.

- Inadequate organ function demonstrated by any of the following, unless due to the underlying disease and approved by the medical monitor:
  - All Parts: Total bilirubin > 1.5 × upper limit of normal (ULN). Total bilirubin > 1.5 × ULN is acceptable if direct bilirubin ≤ 1.2 × ULN or with a diagnosis of Gilbert's syndrome.
  - Parts 1 and 3: Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 × ULN.
  - Parts 2 and 4: AST and ALT > 2.5 × ULN or > 5 × ULN for subjects with liver metastases.
  - All Parts: Creatinine clearance < 50 mL/min based on Cockroft-Gault formula or 24-hour urinalysis (< 30 mL/min for MM).
  - All Parts: Alkaline phosphatase (ALP) ≥ 2.5 × ULN.
    - Subjects with 1) bone metastases AND 2) no hepatic parenchymal metastases on screening radiographic examinations may enroll if ALP is ≤ 5 × ULN. Subjects with 1) bone metastases AND 2) hepatic parenchymal metastases on screening radiographic examinations may enroll if ALP is ≤ 5 × ULN only with medical monitor approval.
- Receipt of anticancer medications or investigational drugs within the following intervals before the first administration of study drug, unless with medical monitor approval:
  - < 5 half-lives or 14 days, whichever is longer, for any investigational agent.
  - < 5 half-lives for all other chemotherapy or targeted small molecule anticancer medications.
  - < 6 weeks for mitomycin-C or nitrosoureas.
  - < 4 weeks for immunotherapy or antibody therapy.
  - The following medications are allowed:
    - Subjects with mCRPC may be maintained on androgen deprivation, chemical or surgical, at the discretion of the investigator, with a castrate level of testosterone documented (< 50 ng/dL) during the screening period and while on study.
    - Low-dose corticosteroids (prednisone or the equivalent ≤ 10 mg per day) may be administered. Use of inhaled or topical steroids and prophylactic corticosteroids for radiographic procedures is permitted.
    - For hematologic malignancies: Hydroxyurea for controlling proliferative disease may be administered. Hydroxyurea should not be used within at least 48 hours before and on the day of the [redacted] sample collection (bone marrow and blood) or during or 72 hours before or after azacitidine administration.
    - For Parts 1 and 2/TGC: Receipt of less than 160 mg dexamethasone within 14 days before receiving the first dose of study drug is allowed.
    - Denosumab and zoledronic acid are permitted to treat cancer-related bone diseases.
- Unless approved by the medical monitor, may not have received an allogeneic hematopoietic stem cell transplant within 6 months before treatment, or have active graft-versus-host-disease following allogeneic transplant, or have received immunosuppressive therapy following allogeneic transplant within 2 weeks of Cycle 1 Day 1.
- Unless approved by the medical monitor, may not have received autologous hematopoietic stem cell transplant within 3 months before treatment.
- Any unresolved toxicity ≥ Grade 2 (except stable Grade 2 peripheral neuropathy or alopecia) from previous anticancer therapy.
- Radiotherapy within the 2 weeks before initiation of treatment. Palliative radiation treatment to nonindex or bone lesions performed less than 2 weeks before treatment initiation may be considered with medical monitor approval. In Part 3/C-ES-TGE and Part 4/C-EX-TGC, MF subjects may not have had splenic irradiation within 6 months of the first dose of INCB057643.

- Type 1 diabetes or uncontrolled Type 2 diabetes.
  - All Parts: HbA1c ≥ 8% (all subjects will have HbA1c test at screening).
  - For Parts 1 and 3 only: fasting blood glucose > 160 mg/dL (> 8.9 mmol/L).
- Known human immunodeficiency virus infection (HIV; HIV 1/2 antibodies).
- Evidence of hepatitis B virus or hepatitis C virus infection.
- Currently active and uncontrolled infectious disease requiring systemic antibiotic, antifungal, or antiviral treatment.
- Untreated brain or central nervous system (CNS) metastases or brain/CNS metastases that have progressed (eg, evidence of new or enlarging brain metastasis or new neurological symptoms attributable to brain/CNS metastases). Subjects with previously treated and clinically stable brain/CNS metastases and off all corticosteroids for ≥ 2 weeks before Cycle 1 Day 1 are eligible. Primary CNS lymphoma will only be permitted in Part 2/TGA. Subjects with glioblastoma are not subjected to this criterion with medical monitor approval.
- History or presence of abnormal ECG that, in the investigator's opinion, is clinically meaningful. A screening QTc interval of > 470 msec is excluded. For subjects with an intraventricular conduction delay (QRS interval ≥ 120 msec) the JTc interval may be used in place of the QTc with sponsor approval. Subjects with left bundle branch block are excluded. Subjects with QTc prolongation due to a pacemaker may enroll if the JT is normal or with medical monitor approval. In the event that a single QTc is > 470 msec, the subject may enroll if the average QTc for the 3 ECGs is < 470 msec.
- Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
- International normalized ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (aPTT) > 1.5 × ULN (unless the subject is receiving anticoagulant therapy, in which case, the subject may be included as long as the INR, PT, and aPTT are within therapeutic range of intended use of anticoagulants).
  Note: Partial thromboplastin time may be used in place of aPTT per institutional standards.
- All parts of the study (where applicable) for solid tumors and lymphomas: Subjects with a history of bleeding related to cancer under study requiring a medical intervention (eg, embolization procedure, red blood cell transfusion, or hospitalization) within 30 days of study enrollment.
- Clinically significant bleeding within 14 days of Cycle 1 Day 1.

INCB057643 Dosage and Mode of Administration:

Part 1 and Part 2 Monotherapy

INCB057643 tablets will be administered orally in 21-day treatment cycles. The starting dose in Part 1/TGA will be 8 mg QD. The starting dose for Part 1/TGB and Part 1/TGC will be the PAD identified in Part 1/TGA. Dose escalation during Part 1 of the study will proceed using the dose-escalation rules described above. The dose of INCB057643 in Part 2 will be the treatment group–specific MTD or PAD identified in Part 1. More than 1 dose of INCB057643 and/or schedule may be assessed in Part 2 pending emerging safety, PK, and PD data.

Subjects will fast least 2 hours before and 1 hour after study drug administration except on days when serial PK and PD sampling is conducted, then subjects will refrain from food consumption at least 8 hours before the study drugs or as indicated in the PK section.

Dose escalations for INCB057643 in Part 1 will be accomplished using the following options: 1) increasing the number of tablets taken at each QD administration, or 2) increasing administration frequency to BID, or 3) increasing the number of tablets taken at 1 or more dose administrations and increasing the frequency to BID. The sponsor may implement alternate administration, such as intermediate doses, alternate dosing schedules, or alternate formulations, depending on PK, PD, and safety results.

Part 3 and Part 4 Combination Therapy

Study Drug

The starting dose of INCB057643 in Part 3 will be the PAD or 1 dose level below the MTD of INCB057643 monotherapy identified in Part 1 of the study. Pending emerging data in Part 1 and Part 2, a lower starting dose of INCB057643 could be selected for all or several combinations in Part 3 (eg, 2 dose levels below the MTD of INCB057643 in Part 1). The 12 mg QD dose of INCB057643 was identified as the MTD in Part 1/TGA; thus the 8 mg QD dose of INCB057643 will be the starting dose for Part 3 C-ES-TGA/TGB/TGC/TGD. The starting dose of INCB057643 in Part 4 will be the treatment group–specific RP2D identified in Part 3. Study drug QD doses will be taken in the morning in a continuous 21- or 28-day treatment cycle depending on the SOC agent administered in combination. The subjects will fast at least 2 hours before and 1 hour after study drug administration except on days when serial PK and PD sampling is conducted, then subjects will fast at least 8 hours before the study drugs or as indicated in the PK sampling section. Subjects will continue to receive combination therapy as long as they are deriving benefit and have not met any of the Protocol-defined conditions for discontinuation of treatment. Intra-subject dose escalation is not permitted in combination therapy treatment groups.

Standard of Care Agents

Conventional regimens of the SOC agents will be used throughout Part 3 and Part 4 of the study. Subjects will continue to receive combination therapy as long as they are deriving benefit and have not met any of the Protocol-defined conditions for discontinuation of treatment. Dosing adjustment (dosing delay and/or dose reduction) during treatment is allowed. Intra-subject dose-escalation is not permitted.

- Gemcitabine (Part 3 Only): Will be administered as 1000 mg/m^2 by a 30-minute intravenous (IV) infusion (± 5 minutes) on Days 1 and 8 of each 21-day cycle. Subjects may receive prophylactic granulocyte colony-stimulating factor (G-CSF) support with filgrastim (Neupogen®) per institutional guidelines, however, it should not be given in the first cycle unless discussed with the medical monitor.
- Paclitaxel (Part 3 Only): Will be administered as 80 mg/m^2 by a 1-hour IV infusion (± 15 min) on Days 1, 8, and 15 of each 21-day cycle. Treatment continuation following clinical response will be at the discretion of the investigator. Subjects must receive premedications (IV or orally [PO]) with corticosteroids, H1- and H2-antagonists, antihistamines, and antiemetics based on institutional guidelines, investigator practice, or local prescribing information or standards of care. Subjects may receive prophylactic G-CSF support with filgrastim (Neupogen) per institutional guidelines, however, it should not be given in the first cycle unless discussed with the medical monitor.
- Rucaparib: Will be administered as 600 mg (two 300 mg tablets) PO BID in a continuous dosing regimen with or without food. This oral agent is prepared as 200, 250, and 300 mg tablets.
- Abiraterone: Will be administered as 1000 mg (two 500 mg tablets or four 250 mg tablets) PO QD in a continuous dosing regimen in combination with prednisone 5 mg PO BID. Abiraterone should be taken on an empty stomach; no food should be consumed for at least 2 hours before the dose is taken and for at least 1 hour after the dose is taken.
- Ruxolitinib: Will be administered as a dose of 5 to 25 mg PO BID in a continuous dosing regimen using the dose designated as the stable dose at the time of screening for each subject. Doses of ruxolitinib should be self-administered approximately 12 hours apart without regard to food.
- Azacitidine: Will be administered as a dose of 75 mg/m^2 IV or subcutaneously for 7 days during a 9-day or less period (ie, a 2-day break allowed on weekend, if needed) of each 28-day treatment cycle.

Study Schedule:

All subjects will have a screening visit, which may occur up to 28 days before enrollment. Screening will begin at the time the subject signs the ICF and will continue until the date the subject is enrolled in the study (Cycle 1 Day 1).

During treatment, subjects will have regularly scheduled study visits as follows:

Part 1 and Part 2 INCB057643 Monotherapy: 21-Day Cycles

- Cycle 1: Days 1, 2, 8 (± 3 days), and 15 (± 3 days)
- Cycle 2 and beyond: Days 1 (± 3 days), 2 (Part 2/TGA; food-effect only), and 11 (± 3 days)

Part 3 (C-ES) and Part 4 (C-EX) INCB057643 Combination Therapy:

- Gemcitabine (Part 3 Only): 21-Day Cycles (Cycles 1 and 2: Days 1, 8 [± 3 days], and 15 [± 3 days]; Cycle 3 and beyond: Days 1 [± 3 days] and 8 [± 3 days])
- Paclitaxel (Part 3 Only): 21-Day Cycles (Cycles 1 and 2: Days 1, 8 [± 3 days], and 15 [± 3 days]; Cycle 3 and beyond: Days 1 [± 3 days], 8 [± 3 days], and 15 [± 3 days])
- Rucaparib: 21-Day Cycles (Cycle 1: Days 1, 8 [± 3 days], and 15 [± 3 days]; Cycle 2 and beyond: Days 1 [± 3 days] and 11 [± 3 days])
- Abiraterone: 21-Day Cycles (Cycle 1: Days 1, 8 [± 3 days], and 15 [± 3 days]; Cycle 2 and beyond: Days 1 [± 3 days] and 11[± 3 days])
- Ruxolitinib: 21-Day Cycles (Cycle 1: Days 1, 8 [± 3 days], and 15 [± 3 days]; Cycle 2 and beyond: Days 1 [± 3 days] and 11 [± 3 days])
- Azacitidine: 28-Day Cycles anchored to azacitidine schedule (Days 1, 8 [± 3 days], 15 [± 3 days], 22 [± 3 days], and 29 to 42)

If a decision is made that the subject will permanently discontinue study drug, the end of treatment (EOT) visit will be conducted. All subjects will have a safety follow-up visit at 30 to 35 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). The end of study (EOS) visit can occur at the same time of the safety follow-up visit unless there is an ongoing SAE or clinically significant AE. In this case, EOS visit will occur when the AE is resolved, returned to baseline, or deemed irreversible per the investigator.

Estimated Duration of Participation:

Subjects will be treated in 21- or 28-day cycle depending on treatment regimens until they meet withdrawal criteria. Treatment duration will vary significantly between subjects, but is expected to average approximately 4 to 6 months.

Estimated Number of Subjects:

- Part 1: 3 to 10 subjects per cohort per treatment group (3 treatment groups/approximately 60 subjects).
- Part 2: 225 subjects across 3 treatment groups.
- Part 3: Approximately 3 to 10 subjects per cohort per treatment group (6 treatment groups/ approximately 60 subjects).
- Part 4: Approximately 71 subjects across 4 treatment groups.

Statistical Methods:

Part 1 of the study is a standard dose-escalation design, and the sample size depends on the occurrence of DLTs. Approximately 3 to 6 subjects will be enrolled in each dose level.

Part 2/TGA will enroll up to approximately 165 subjects with specified solid tumors or lymphoma. Approximately 5 to 15 subjects will be enrolled in the pancreatic adenocarcinoma, breast cancer, glioblastoma multiforme, Ewing's sarcoma, and NHL groups. The high-grade serous ovarian cancer and mCRPC groups will include approximately 20 subjects. The group of any other solid tumor or lymphoma (except the specified) with any pathway alteration relevant to BET protein signaling, [redacted], will enroll up to 20 subjects as well.

Part 2/TGB will enroll up to 45 subjects with AML, HR- MDS, MDS/MPN, or MF; and Part 2/TGC will

enroll up to 15 subjects with MM. This will provide > 80% chance of detecting at least 1 responder if the underlying response rate is 30%.

Part 3 will use a 3 + 3 design to evaluate different doses of INCB057643 in combination with gemcitabine, paclitaxel, rucaparib, abiraterone, ruxolitinib, or azacitidine in 6 treatment groups. Dose escalation for 6 treatment groups will proceed independently. Approximately 3 to 6 subjects will be enrolled in each dose level for each treatment group. The total number of subjects will depend on the frequency of DLTs and the number of dose levels tested before the MTD and RP2D are reached.

In Part 4, approximately 71 subjects will be enrolled across 4 possible expansion treatment groups to further evaluate the safety, tolerability, efficacy, PK, and PD of the RP2Ds selected from Part 3. The high-grade serous ovarian cancer and mCRPC cohorts will include approximately 20 subjects. The MF group will enroll approximately 16 subjects. The AML/HR-MDS cohort will enroll approximately 15 subjects.

Descriptive statistics will be provided where appropriate. Continuous endpoints will be summarized with number of subjects, mean, standard deviation, minimum, median, and maximum for each cohort. Categorical endpoints will be summarized with frequency and percentages for each category by cohort. The clinical safety data (vital signs, ECGs, routine laboratory tests, and AEs) will be summarized descriptively.

Objective response rate will be estimated with a 95% exact confidence interval (CI).

TABLE OF CONTENTS

SYNOPSIS 3
LIST OF ABBREVIATIONS 25
1. INTRODUCTION 30
1.1. Background 30
1.2. Overview of INCB057643 32
1.2.1. Nonclinical Pharmacology of INCB057643 32
1.2.2. Nonclinical Drug Metabolism and Pharmacokinetics of INCB057643 33
1.3. Overview of Standard-of-Care Agents Selected For Combination Therapies 34
1.3.1. Overview of Gemcitabine in Solid Tumors Including Ovarian Cancer 34
1.3.2. Overview of Paclitaxel in Solid Tumors Including Ovarian Cancer 35
1.3.3. Overview of Rucaparib in Ovarian Cancer 36
1.3.4. Overview of Abiraterone in Metastatic Castration-Resistant Prostate Cancer 36
1.3.5. Overview of Azacitidine in Acute Myeloid Leukemia and Myelodysplastic Syndrome 37
1.3.6. Overview of Ruxolitinib in Myelofibrosis 37
1.4. Study Rationale 38
1.4.1. Rationale for Combining INCB57643 With Gemcitabine and Paclitaxel in Ovarian Cancer 38
1.4.2. Rationale for Combining INCB57643 With Rucaparib in Ovarian Cancer 39
1.4.3. Rationale for Combining INCB57643 With Abiraterone in Castration-Resistant Prostate Cancer 39
1.4.4. Rationale for Combining INCB57643 With Ruxolitinib in Myelofibrosis 40
1.4.5. Rationale for Combining INCB57643 With Azacitidine in Acute Myeloid Leukemia/High-Risk Myelodysplastic Syndrome 40
1.5. INCB057643 Safety and Potential Risks 41
1.5.1. Preclinical Safety and Risks 41
1.5.2. Potential Risks of Gemcitabine 42
1.5.3. Potential Risks of Paclitaxel 42
1.5.4. Potential Risks of Rucaparib 43
1.5.5. Potentials Risks of Abiraterone 43
1.5.6. Potential Risks of Ruxolitinib 43
1.5.7. Potential Risks of Azacitidine 43
1.5.8. Potential Risks of Combination Therapy 44

1.6. Clinical Experience With INCB057643 in Study INCB 57643-101 44
1.6.1. Clinical Pharmacokinetics and Pharmacodynamics 44
1.6.2. Clinical Trial Experience 47
1.6.2.1. Dose-Escalation and Expansion, Safety, and Tolerability Study of INCB057643 in Subjects With Advanced Malignancies 47
2. STUDY OBJECTIVES AND ENDPOINTS 53
2.1. Study Objectives 53
2.1.1. Primary Objectives 53
2.1.2. Secondary Objectives 53
[redacted] [redacted] 53
2.2. Study Endpoints 53
2.2.1. Primary Endpoints 53
2.2.2. Secondary Endpoints 53
[redacted] [redacted] 54
3. SUBJECT ELIGIBILITY 54
3.1. Subject Inclusion Criteria 54
3.2. Subject Exclusion Criteria 58
4. INVESTIGATIONAL PLAN 61
4.1. Overall Study Design 61
4.1.1. Part 1 – Monotherapy Dose Escalation 62
4.1.2. Part 2 – Monotherapy Dose Expansion 63
4.1.3. Part 3 – Combination Dose Escalation (C-ES) 65
4.1.4. Part 4 – Combination Dose Expansion (C-EX) 66
4.2. Number of Subjects 66
4.2.1. Planned Number of Subjects 66
4.2.2. Replacement of Subjects 67
4.3. Measures Taken to Avoid Bias 67
4.4. Duration of Treatment and Subject Participation 67
4.5. Overall Study Duration 67
4.6. Study Termination 67
5. TREATMENT 68
5.1. Treatment Assignment 68
5.1.1. Subject Numbering and Treatment Assignment 68

5.1.2. Randomization and Blinding 68
5.2. Study Drugs 68
5.2.1. INCB057643 68
5.2.1.1. Description and Administration 68
5.2.1.2. Supply, Packaging, and Labeling 69
5.2.1.3. Storage 69
5.2.1.4. Dispensing Study Drug 69
5.2.1.5. Instruction to Subjects for Handling Study Drug 69
5.2.2. Standard of Care Agents 70
5.2.2.1. Gemcitabine Administration 70
5.2.2.2. Paclitaxel Administration 70
5.2.2.3. Rucaparib Administration 70
5.2.2.4. Abiraterone Administration 70
5.2.2.5. Ruxolitinib Administration 70
5.2.2.6. Azacitidine Administration 71
5.2.2.7. Supply, Packaging, and Labeling 71
5.3. Treatment Compliance 71
5.4. Dose Modifications 72
5.4.1. Study Drug – Part 1 and Part 3 72
5.4.1.1. Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose 72
5.4.1.2. Management of Dose-Limiting Toxicities or Other Urgent Situations 73
5.4.1.3. Follow-Up of Dose-Limiting Toxicities 73
5.4.1.4. Procedures for Cohort Review and Dose Escalation 73
5.4.2. INCB057643 Dose Interruptions and Reductions 74
5.4.3. Standard of Care Agent Dose Interruptions and Reductions 78
5.4.3.1. Specific Guidelines for Gemcitabine and Paclitaxel in Solid Tumors 78
5.4.4. Criteria for Permanent Discontinuation of INCB057643 79
5.4.5. Criteria and Procedures for Dose Escalations of INCB057643 79
5.5. Withdrawal of Subjects From Study Treatment 80
5.5.1. Withdrawal Criteria 80
5.5.2. Withdrawal Procedures 80
5.6. Concomitant Medications 81
5.6.1. Restricted Medications 81

5.6.2. Prohibited Medications 82
6. STUDY ASSESSMENTS 82
6.1. Screening 110
6.2. Treatment 111
6.2.1. Day 1 111
6.2.2. Visit Scheduling 111
6.3. End of Treatment 111
6.4. Follow-Up 112
6.4.1. Safety Follow-Up 112
6.4.2. Unscheduled Visits 112
7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES 112
7.1. Administration of Informed Consent Form 112
7.2. Interactive Response Technology Procedure 112
7.3. Demography and Medical History 112
7.3.1. Transfusion History Status (Myelofibrosis Combination Cohorts Only) 113
7.3.2. Screening Symptom Form (Myelofibrosis Combination Cohorts Only) 113
7.4. Prior and Concomitant Medications and Procedures 113
7.5. Safety Assessments 113
7.5.1. Adverse Events 113
7.5.2. Physical Examinations 113
7.5.2.1. Comprehensive Physical Examination 114
7.5.2.2. Targeted Physical Examination 114
7.5.3. Vital Signs and Weight 114
7.5.4. Cardiac Monitoring 114
7.5.4.1. Twelve-Lead Electrocardiograms 114
7.5.4.2. Electrocardiogram Procedures 114
7.5.4.3. Additional Instructions for Timed Electrocardiograms (Part 1 and Part 2 Only) 114
7.5.4.4. Echocardiogram or MUGA 115
7.5.5. Laboratory Assessments 115
7.5.5.1. Chemistry, Hematology, Urinalysis, Coagulation Panel, Factor VII, Serology, and Endocrine Function Testing 115
7.5.5.2. Pregnancy Testing 115

7.5.5.3. Hepatitis Screening Tests 115
7.5.5.4. Cardiac Troponin (Either T or I) Testing 116
7.6. Performance and Health-Related Quality of Life Assessments 116
7.6.1. ECOG Performance Status 116
7.7. Efficacy Assessments 116
7.7.1. Lymphoma, Chronic Lymphocytic Leukemia, and Myelofibrosis: CT Scan or MRI 117
7.7.1.1. MRI or CT Scan in Myelofibrosis Combination Cohort Subjects 117
7.7.2. Lymphoma: FDG-PET or Combined PET-CT 118
7.7.3. Solid Tumors and Lymphoma: Tumor Biopsy 118
7.7.4. Leukemia, High-Risk Myelodysplastic Syndrome, Myelodysplastic Syndrome/Myeloproliferative Neoplasm, Myelofibrosis, and Multiple Myeloma: Bone Marrow Biopsy 118
7.7.5. Leukemia and Lymphoma: Immunophenotyping 119
7.7.6. Leukemia, HR-MDS, and MDS/MPN: Peripheral Blood Blast Counts 119
7.7.7. Multiple Myeloma: Disease Assessment 119
7.7.8. Multiple Myeloma: Skeletal Survey 119
7.7.9. Myelofibrosis: Spleen Palpitation (Myelofibrosis Combination Cohorts Only) 119
7.7.10. Castrate Resistant Prostate Cancer: Prostate Cancer Clinical Trials Work Group 3 120
7.8. Pharmacokinetic Assessments 120
7.8.1. Blood Sample Collection 120
7.8.2. Urine Sample Collection 120
7.8.3. Bioanalytical Methodology and Analysis 121
7.8.4. Food-Effect Pharmacokinetic Testing 121
[redacted] 121
[redacted] 121
[redacted] 122
[redacted] 122
[redacted] 122
[redacted] 122
[redacted] 122

[redacted] [redacted] .122
[redacted] [redacted] .123
[redacted] [redacted] 123
[redacted] [redacted] 124
7.10. Other Study Procedures 124
7.10.1. Distribution of Subject Reminder Cards 124
8. SAFETY MONITORING AND REPORTING 124
8.1. Adverse Events 124
8.1.1. Definitions 124
8.1.2. Reporting 124
8.2. Laboratory Test Abnormalities 126
8.3. Serious Adverse Events 126
8.3.1. Definitions 126
8.3.2. Reporting 127
8.4. Emergency Unblinding of Treatment Assignment 128
8.5. Pregnancy 128
8.6. Warnings and Precautions 128
8.7. Data Monitoring Committee 128
8.8. Product Complaints 128
9. STATISTICS 129
9.1. Study Populations 129
9.2. Selection of Sample Size 129
9.3. Level of Significance 130
9.4. Statistical Analyses 130
9.4.1. Efficacy Analyses 130
9.4.1.1. Primary Efficacy Analyses 130
9.4.1.2. Secondary Efficacy Analyses 130
[redacted] [redacted] 130
9.4.2. Safety Analyses 131
9.4.2.1. Adverse Events 131
9.4.2.2. Clinical Laboratory Tests 131
9.4.2.3. Vital Signs 131

9.4.2.4. Electrocardiograms 132
9.4.3. Pharmacokinetic Analysis 132
9.4.4. Pharmacodynamic Analysis 132
9.5. Analyses for the Data Monitoring Committee 133
9.6. Interim Analysis 133
10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES 133
10.1. Investigator Responsibilities 133
10.2. Accountability, Handling, and Disposal of Study Drug 135
10.3. Data Management 135
10.4. Data Privacy and Confidentiality of Study Records 136
10.5. Financial Disclosure 136
10.6. Publication Policy 137
11. REFERENCES 138
APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS 144
APPENDIX B. PHARMACOKINETIC ANALYTICAL PARAMETERS 145
APPENDIX C. EASTERN COOPERATIVE ONCOLOGYGROUP PEFORMANCE STATUS 146
APPENDIX D. INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR ACUTE MYELOID LEUKEMIA 147
APPENDIX E. RESPONSE CRITERIA FOR GLIOBLASTOMA 148
APPENDIX F. INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR MYELODYSPLASTIC SYNDROME 151
APPENDIX G. INTERNATIONAL CONSORTIUM PROPOSAL OF UNIFORM RESPONSE CRITERIA FOR MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS IN ADULTS 152
APPENDIX H. REVISED RESPONSE CRITERIA FOR MYELOFIBROSIS: INTERNATIONAL WORKING GROUP-MYELOPROLIFERATIVE NEOPLASMS RESEARCH AND EUROPEAN LEUKEMIANET CONSENSUS REPORT 155
APPENDIX I. INTERNATIONAL UNIFORM RESPONSE CRITERIA FOR MULTIPLE MYELOMA 157
APPENDIX J. CRITERIA FOR EVALUATING DISEASE RESPONSE AND PROGRESSION IN SUBJECTS WITH MULTIPLE MYELOMA TREATED BY HIGH-DOSE THERAPY AND HAEMOPOIETIC STEM

CELL TRANSPLANTATION: MYELOMA SUBCOMMITTEE OF THE EUROPEAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION 158

APPENDIX K. RESPONSE CRITERIA FOR LYMPHOMA – THE LUGANO CLASSIFICATION 159

APPENDIX L. RESPONSE ASSESSMENT IN WALDENSTRÖM MACROGLOBULINEMIA 161

APPENDIX M. RESPONSE ASSESSMENT IN CHRONIC LYMPHOCYTIC LEUKEMIA 162

APPENDIX N. PROSTATE CANCER WORKING GROUP 3 GUIDELINES 164

APPENDIX O. CYP3A4 INHIBITORS AND INDUCERS 170

APPENDIX P. SCREENING SYMPTOM FORM 177

APPENDIX Q. MANAGEMENT OF POTENTIAL HY'S LAW CASES 179

APPENDIX R. PROTOCOL AMENDMENT SUMMARY OF CHANGES 183

LIST OF TABLES

Table 1: INCB057643 (Parent) and INCB057228 (M2) Steady-State (Cycle 1 Day 8) Pharmacokinetic Parameters....45

Table 2: The Effect of a High-Fat Meal on the Pharmacokinetics of INCB057643 (12 mg) and INCB057228 (M2)....46

Table 3: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 2 Subjects in Study INCB 57643-101 Part 1 Treatment Group A by MedDRA Preferred Term in Decreasing Order of Frequency (Safety Evaluable Population)....48

Table 4: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 2 Subjects in Study INCB 57643-101 Part 1 Treatment Group B by MedDRA Preferred Term in Decreasing Order of Frequency (Safety Evaluable Population)....50

Table 5: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 10% of Subjects in Study INCB 57643-101 Part 2/Treatment Group A by MedDRA Preferred Term in Decreasing Order of Frequency (Safety Evaluable Population)....51

Table 6: Standard of Care Agent Administration....71

Table 7: Definition of Dose-Limiting Toxicity....73

Table 8: Guidelines for Interruption and Restarting of INCB057643....74

Table 9: Schedule of Assessments – Monotherapy INCB057643 (Part 1 and Part 2; All Treatment Groups)....83

Table 10: Schedule of Laboratory Assessments – Monotherapy INCB057643 (Part 1 and Part 2; All Treatment Groups)....85

Table 11: Schedule of Assessments – Combination INCB057643 and Gemcitabine (Part 3 C-ES-TGA)....87

Table 12: Schedule of Laboratory Assessments – Combination INCB057643 and Gemcitabine (Part 3 C-ES-TGA)....88

Table 13: Schedule of Timed Pharmacokinetic Assessments – Combination INCB057643 and Gemcitabine (Part 3 C-ES-TGA)....89

Table 14: Schedule of Assessments – Combination INCB057643 and Paclitaxel (Part 3 C-ES-TGB)....90

Table 15: Schedule of Laboratory Assessments – Combination INCB057643 and Paclitaxel (Part 3 C-ES-TGB)....91

Table 16: Schedule of Timed Pharmacokinetic Assessments – Combination INCB057643 and Paclitaxel (Part 3 C-ES-TGB)....92

Table 17: Schedule of Assessments – Combination INCB057643 and Rucaparib (Part 3 C-ES-TGC and Part 4 C-EX-TGA)....93

Table 18: Schedule of Laboratory Assessments – Combination INCB057643 and Rucaparib (Part 3 C-ES-TGC and Part 4 C-EX-TGA)....94

Table 19: Schedule of Timed Pharmacokinetic Assessments – Combination INCB057643 and Rucaparib (Part 3 C-ES-TGC and Part 4 C-EX-TGA) 95
Table 20: Schedule of Assessments – Combination INCB057643 and Abiraterone (Part 3 C-ES-TGD and Part 4 C-EX-TGB) 96
Table 21: Schedule of Laboratory Assessments – Combination INCB057643 and Abiraterone (Part 3 C-ES-TGD and Part 4 C-EX-TGB) 98
Table 22: Schedule of Timed Pharmacokinetic Assessments – Combination INCB057643 and Abiraterone (Part 3 C-ES-TGD and Part 4 C-EX-TGB).....99
Table 23: Schedule of Assessments – Combination INCB057643 and Ruxolitinib (Part 3 C-ES-TGE and Part 4 C-EX-TGC).....100
Table 24: Schedule of Laboratory Assessments – Combination INCB057643 and Ruxolitinib (Part 3 C-ES-TGE and Part 4 C-EX-TGC) 102
Table 25: Schedule of Timed Pharmacokinetic Assessments – Combination INCB057643 and Ruxolitinib (Part 3 C-ES-TGE and Part 4 C-EX-TGC) 104
Table 26: Schedule of Assessments – Combination INCB057643 and Azacitidine (Part 3 C-ES-TGF and Part 4 C-EX-TGD).....105
Table 27: Schedule of Laboratory Assessments – Combination INCB057643 and Azacitidine (Part 3 C-ES-TGF and Part 4 C-EX-TGD) 107
Table 28: Schedule of Timed Pharmacokinetic Assessments – Combination INCB057643 and Azacitidine (Part 3 C-ES-TGF and Part 4 C-EX-TGD).....108
Table 29: Schedule of Timed Translational/Pharmacodynamic Assessments – Combination INCB057643 and Azacitidine (Part 3 C-ES-TGF and Part 4 C-EX-TGD) 109
Table 30: Local Laboratory Tests: Required Analytes 110
Table 31: Required Analytes for Multiple Myeloma Subjects 119
Table 32: Probability of Dose Escalation by DLT Rate 129
Table 33: Criteria for Clinically Notable Vital Sign Abnormalities.....131
Table 34: Criteria for Clinically Notable Electrocardiogram Abnormalities 132

LIST OF FIGURES

Figure 1: Composite PK-PD Curve for Subjects in Study INCB 57643-101 (N = 67) 47
Figure 2: Part 1 and Part 2 Monotherapy Dose Escalation and Expansion Study Design.....64
Figure 3: Part 3 Combination Dose Escalation Study Design 65
Figure 4: Part 4 Combination Dose Expansion Study Design 66

LIST OF ABBREVIATIONS

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

Abbreviation	Explanation
ADT	androgen deprivation therapy
AE	adverse event
A_e	amount of drug excreted in urine over sampling interval
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AR	androgen receptor
AR-V7	androgen receptor splice variant 7
AST	aspartate aminotransferase
AUC	area under the plasma or serum concentration-time curve
$AUC_{0-\tau}$	area under the steady-state plasma or serum concentration-time curve over 1 dosing interval (ie, from Hour 0 to 12 for BID administration or from Hour 0 to 24 for QD administration)
AUC_{0-t}	area under the single-dose plasma or serum concentration-time curve from Hour 0 to the last quantifiable measurable plasma concentration
BCLU	B-cell lymphoma, unclassifiable
BD	bromodomain
BET	bromodomain and extra-terminal
BID	twice daily
BOR	best overall response
BRD	bromodomain-containing protein
BRDT	bromodomain testis-specific protein
C_{ave}	average steady-state plasma concentration
CBC	complete blood count
C-ES	combination dose escalation
C-EX	combination dose expansion
CI	confidence interval
Cl/F	oral dose clearance
CLL	chronic lymphocytic leukemia
Cl_r	renal clearance

Abbreviation	Explanation
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
c-MYC	cellular form of a regulator gene that can act as an oncogene (MYC)
c-Myc	transcription factor encoded by the c-MYC gene
CNS	central nervous system
CR	complete response/remission
CRi	complete response with incomplete recovery
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CYP	cytochrome P450
CYP17	17 α-hydroxylase/C17, 20-lyase
DHEA	dehydroepiandrosterone
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EBMT	European Society for Blood and Marrow Transplantation
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELN	European LeukemiaNet
EOT	end of treatment
FDA	Food and Drug Administration
FDG	[^{18}F] fluorodeoxyglucose
f_e	percent excreted in urine
FISH	fluorescence *in situ* hybridization
FLAIR	fluid-attenuated inversion recovery
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GLP	Good Laboratory Practices

Abbreviation	Explanation
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
Hgb	hemoglobin
HI	hematological improvement
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HR-MDS	high-risk myelodysplastic syndrome
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IL	interleukin
IN	Investigator Notification
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
IWG	International Working Group
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
JAK	Janus kinase
L-DAC	low-dose cytarabine
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LOH	loss of heterozygosity
MCP	methyl-accepting chemotaxis protein
mCRPC	metastatic castration-resistant prostate cancer
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MM	multiple myeloma
mOS	median overall survival
mPFS	median progression-free survival

Abbreviation	Explanation
MPN	myeloproliferative neoplasm
MPN-SAF TSS	Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NHL	non-Hodgkin's lymphoma
NMC	nuclear protein in testis midline carcinoma
NSCLC	non–small-cell lung cancer
NTD	nontolerated dose
NUT	nuclear protein in testis (gene)
OAT	organic anion transporter
OATP	organic anion transporter polypeptide
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
PAD	pharmacologically active dose
PARP	Poly (adenosine diphosphate-ribose) polymerase
PCR	polymerase chain reaction
PCWG3	Prostate Cancer Working Group 3
PD	pharmacodynamic
PET	positron emission tomography
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PK	pharmacokinetic
PO	orally
PR	partial response/remission
PRBC	packed red blood cell
PSA	prostate-specific antigen
PT	prothrombin time
QD	once daily
RANO	Response Assessment in Neuro-Oncology
RBC	red blood cell
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid

Abbreviation	Explanation
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SC	subcutaneous
sCR	stringent complete response
SD	stable disease
SmPC	Summary of Product Characteristics
SOC	standard of care
SOP	standard operating procedure
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent plasma terminal phase disposition half-life
TEAE	treatment-emergent adverse event
TGA	Treatment Group A
TGB	Treatment Group B
TGC	Treatment Group C
TGD	Treatment Group D
TGE	Treatment Group E
TGF	Treatment Group F
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
USPI	United States Prescribing Information
VGPR	very good partial response
V_z/F	apparent oral dose volume of distribution
WBC	white blood cell
WHO	World Health Organization
λ_z	apparent terminal-phase disposition rate constant

1. INTRODUCTION

INCB 57643-101 is a 2-part, open-label, dose-escalation/dose-expansion study evaluating INCB057643 in subjects with advanced malignancies. Part 1 of the study will determine the maximum tolerated dose (MTD) of INCB057643 in 3 disease-specific treatment groups. Part 2 will evaluate the safety, preliminary efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of the treatment group–specific dose selected in Part 1 in tumor types postulated to be particularly susceptible to inhibition of bromodomain and extra-terminal (BET) proteins. Part 3 will determine the MTD and recommended Phase 2 dose (RP2D) of INCB057643 in combination with select standard of care (SOC) agents across 6 disease-specific treatment groups. Part 4 will further evaluate the safety, preliminary efficacy, and PK of the treatment group combination of the RP2D identified in Part 3 for select tumor types.

1.1. Background

Central to the evolution of neoplastic cells is a changing pattern of gene expression that distinguishes cancer cells from their normal counterparts. Activation of transcription factors that regulate oncogenic processes, including c-Myc and nuclear factor κB (NF-κB), is frequently observed in human cancers; however, direct targeting of these proteins has remained elusive. Gene expression is also regulated at the level of chromatin by covalent modifications, including histone acetylation and methylation, which specify an "epigenetic code" that regulates the interactions of DNA-binding proteins, nucleosome remodeling complexes, and transcriptional regulators with chromatin (Portela et al 2010). In malignant cells, aberrant changes in epigenetic patterns translate to altered transcriptional profiles. In many cases, these altered epigenetic patterns arise from mutations in genes encoding epigenetic regulator proteins, and mutant epigenetic proteins can be bona fide oncogenes (You and Jones 2012). Thus genetic and epigenetic mechanisms cooperate to promote the development and progression of cancer. A key step in translating the epigenetic code is the recognition of modified histone residues by effector proteins that harbor specific interaction domains.

The BET family of proteins consists of 4 members (bromodomain-containing protein [BRD]2, BRD3, BRD4, and bromodomain testis-specific protein [BRDT]) that each have 2 bromodomain (BD) modules (BD1 and BD2). These BDs exhibit high selectivity for acetylated lysine residues in histones and other proteins. The human genome encodes 61 distinct BDs, but the BET protein modules BD1 and BD2 are distinguishable from other BDs by their higher affinity for di-acetylated lysine motifs (Filippakopoulos and Knapp 2014). Bromodomain testis-specific protein is restricted to germ cells; however, BRD2, BRD3, and BRD4 are ubiquitously expressed. The BET proteins function as transcriptional regulators by binding to acetylation marks in chromatin at gene promoter and enhancer elements and recruiting transcription initiation and elongation complexes such as Mediator, polymerase-associated factor complex, and super elongation complex (Wu and Chiang 2007, Dawson et al 2011). Thus, for many gene promoters and enhancers, BET proteins play a crucial role in linking acetylated chromatin marks to transcriptional activation.

Although BET proteins are found to be associated with thousands of gene promoters and enhancers in the genome, functional studies have revealed that only a subset of these genes are significantly regulated by BET proteins. These genes are transcriptionally controlled by "super

enhancers" that are notable for a high density of BRD4 binding. Many super-enhancer–regulated genes contribute to the development of neoplastic behavior either directly or as a result of chromosomal translocation that leads to dysregulated expression of oncogenes from these elements, such as in the case of the t(8,14) translocation in multiple myeloma (MM) and Burkitt's lymphoma where c-MYC is fused to the immunoglobin heavy chain enhancer. Transcriptional profiling data show that BRD4-dependent genes include many highly regulated genes involved in cell proliferation, differentiation, and survival; however, BRD4 does not regulate expression of constitutively expressed housekeeping genes (Mochizuki et al 2008, Delmore et al 2011). In view of the critical role of BET in regulating expression of cell fate-determining and cell cycle-associated genes, targeted inhibition of BET proteins may have selective pharmacological effects on cancer cells.

The carcinogenic role of the BET protein family is exemplified by a highly malignant, but rare, form of epithelial neoplasia called nuclear protein in testis (NUT) midline carcinoma (NMC) in which a recurrent translocation of BRD3 or BRD4 with NUT creates a novel fusion oncogene, BRD-NUT (French et al 2008). NUT midline carcinoma is characterized by proliferation of undifferentiated epithelial cells resulting from aberrant transcriptional regulation by the mutant oncoprotein (Yan et al 2011). Treatment with the BET-selective inhibitor JQ-1 displaces BRD-NUT from chromatin in patient-derived NMC cells, restores terminal squamous cell differentiation *in vitro*, and provides tumor growth suppression *in vivo* (Filippakopoulos et al 2010). These data support the idea that altered gene transcription associated with BET activity in cancer cells is reversible and provide validation that BET protein inhibition can be efficacious against malignant cells.

In preclinical studies, BET inhibitors have demonstrated efficacy across a wide range of hematologic cancer and solid tumor models. Tumor types associated with dysregulation of transcription factors appear to be highly responsive to BET inhibition. For example, androgen receptor (AR)–dependent prostate cancer cells are highly sensitive to JQ-1 treatment compared with prostate cell lines without androgen dependence (Wyce et al 2013, Asangani et al 2014). Bromodomain-containing protein 4 was shown to directly regulate transcriptional activity of AR, and JQ-1 treatment dissociated AR binding from chromatin leading to downregulation of AR target genes and inhibition of cell growth. These data suggest that combining BET inhibitors with anti-androgens has the potential to suppress AR dependent activity by distinct mechanisms and can counteract mutants such as androgen receptor splice variant 7 (AR-V7) that are resistant to AR blockade (Asangani et al 2014). Furthermore, experiments using patient-derived cells from tumors associated with activation of the Hedgehog-GLI1 pathway shows that BET inhibition reduces growth and downregulates GLI target genes (Tang et al 2014). Finally, the c-MYC oncogene is upregulated in many cancers secondarily (such as in carcinomas of the breast, colon, cervix, and lung) or directly through chromosomal translocations (such as in MM and double-hit and Burkitt's lymphomas). In preclinical models of MYC-dependent neoplasms including KRAS-mutant lung, aggressive lymphoma, acute myeloid leukemia (AML), and t(8;14) MM, BET inhibition was shown to be efficacious *in vivo* (Shimamura et al 2013, Delmore et al 2011). In a model of AML, combination of a BET inhibitor with the epigenetic cancer agent 5-azacytidine was shown to suppress tumor growth greater than individual agents. Another example is Ewing's sarcoma, where expression of fusion transcription factors caused by the translocation of EWS and ETS genes results in global epigenetic reprogramming. These changes are associated with the expression of an oncogenic program that characterizes Ewing's

sarcoma. Treatment of Ewing cell lines with BET inhibitors was shown to block EWS-ETS dependent transcription and to reduce the growth of these cells and tumors *in vitro* and *in vivo* (Hensel et al 2016). These data suggest a therapeutic role for BET inhibitors across a wide range of cancers and demonstrate that neoplasms derived from aberrant activity of lineage-determining transcription factors may be particularly responsive.

Preclinical studies also showed that BET inhibitors acted synergistically with poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor in homologous recombination–proficient cancer cells through BET inhibitor–induced reduction of homologous recombination function and enhanced PARP inhibitor–induced DNA damage in cancer cells (Yang et al 2017). Bromodomain and extra-terminal inhibitors were shown to impair the transcription of *BRCA1* and *RAD51*, which are essential for the homologous recombination function, and to sensitize homologous recombination–proficient tumors, such as breast and ovarian cancers, to poly (adenosine diphosphate-ribose) polymerase (PARP) inhibition.

Finally, targeting BET proteins may have effects beyond direct inhibition of malignant cell growth. Bromodomain-containing protein 2, BRD3, and BRD4 have been shown to be critical for regulating the inflammatory response in several model systems (Belkina et al 2013). Bromodomain and extra-terminal inhibitors exhibited a protective effect *in vivo* against endotoxic shock by reducing the global inflammatory response (Nicodeme et al 2010). Mechanistically, BRD4 has been shown to facilitate transcription by the NF-κB complex (Huang et al 2009). In lymphoma cells characterized by NF-κB pathway activation, BET inhibition reduces the NF-κB transcriptional signature, including proinflammatory genes interleukin (IL)-6 and IL-10 (Ceribelli et al 2014). These studies demonstrate the potential for BET inhibition in reducing the inflammatory response. Tumor-associated inflammation is a hallmark of cancer, and elevated levels of proinflammatory proteins, including IL-6, have been shown to promote multiple aspects of tumorigenesis (Landskron et al 2014). Thus, antitumor activity of BET inhibitors may result from modulation of inflammation in addition to direct effects on the tumor cell. These data warrant evaluation of BET inhibitors in malignancies characterized by underlying inflammation, such as myeloproliferative neoplasms (MPNs), including primary myelofibrosis (MF). Combination of the Janus kinase (JAK) inhibitor ruxolitinib with BET inhibitors is synergistic in models of JAK2V617F positive post-MPN secondary AML, in part, through greater suppression of signal transducer and activator of transcription (STAT)-dependent signaling pathways.

In summary, inhibition of BET protein activity either alone or in combination with SOC agents may have therapeutic utility in diseases such as cancer, where altered expression of growth-promoting, proinflammatory, and survival genes contributes to the establishment and persistence of the oncogenic phenotype.

1.2. Overview of INCB057643

1.2.1. Nonclinical Pharmacology of INCB057643

In vitro, INCB057643 inhibited binding of BET proteins to acetylated histone H4 peptide. The IC_{50} values for BRD4BD1 and BRD4BD2 are 39 ± 6 and 6 ± 1 nM (mean ± SD), respectively. INCB057643 also inhibited BRD2, BRD3, and with lower potency, BRDT, in biochemical assays. When evaluated against 32 distinct BDs from 25 human proteins, INCB057643

exhibited selectivity for BET family BDs. In cellular assays, INCB057643 suppressed the c-MYC protein, a BRD4 target, in KMS12BM MM cells, with an IC_{50} value of 111 ± 41 nM. Many cancer cells derived from hematologic malignancies showed sensitivity to INCB057643 in viability assays, and cells treated with INCB057643 exhibited G1 cell cycle arrest and, in some examples, apoptotic cell death. Multiple myeloma and AML cell lines showed the greatest sensitivity, in general, with IC_{50} values for growth inhibition generally < 200 nM. In contrast, INCB057643 inhibited the proliferation of IL-2–stimulated T cells from normal donors with a potency of 494 ± 118 nM (mean ± SD). The growth of a number of solid tumor cell lines from colon, lung, and breast cancer were also inhibited by INCB057643. In an assay to estimate potency in the presence of human serum proteins, INCB057643 suppressed c-Myc protein levels in myeloma cells spiked into human whole blood, with an IC_{50} value of 55 nM. INCB057643 also suppressed the induction of endogenous methyl-accepting chemotaxis protein (MCP)-1 and MCP-3 from human whole blood that was stimulated *ex viv*o with lipopolysaccharide. The IC_{50} values of 40 nM and 39 nM for MCP-1 and MCP-3, respectively, are similar to the c-Myc whole blood IC_{50} value. These data demonstrate that INCB057643 inhibits BET proteins *in vitro* and in cellular assays, and that inhibition of BET proteins results in the arrest and, in some models, death of cancer cells.

In vivo, INCB057643 inhibited the growth of several tumor models in mice at tolerated, oral doses. In the MM1.S model of MM, a single dose of INCB057643 suppressed c-Myc protein levels in tumor cells in a dose-dependent manner. Tumor PK-PD analysis revealed an *in vivo* IC_{50} value of 367 nM for c-Myc suppression in the MM1.S MM model. The growth of established human tumors was suppressed significantly by INCB057643 when administered as a single agent in the MM1.S MM, MOLM-16 AML, WILL2 lymphoma, H526 SCLC, and RKO colon cancer subcutaneous (SC) xenograft models in immunocompromised mice at 3 mg/kg to 20 mg/kg administered once daily (QD) or 1 mg/kg to 3 mg/kg administered twice daily (BID) orally. Pharmacokinetic-efficacy analyses suggested that maximum tumor growth inhibition was observed when plasma levels of INCB057643 exceeded the *in vivo* IC_{50} for nearly 12 hours. Refer to the Investigator's Brochure (IB) for additional details.

1.2.2. Nonclinical Drug Metabolism and Pharmacokinetics of INCB057643

The absorption, distribution, metabolism, and excretion of INCB057643 have been characterized in rats, dogs, and monkeys. Following intravenous (IV) administration, the systemic clearance was moderate in rats (36% hepatic blood flow) and low in dogs and monkeys (4.1% and 13% of hepatic blood flow, respectively). The steady-state volume of distribution was moderate in rats and monkeys (2.6 and 2.8 L/kg, respectively), but low in dogs (0.66 L/kg). The terminal elimination half-life was moderate, estimated to be approximately 4.3 hours in rats, 7.1 hours in dogs, and 7.0 hours in monkeys. INCB057643 has low to moderate renal excretion; the administered dose excreted in urine as parent varied from 12.5% in monkeys, to 17.6% in rats and 26.1% in dogs. After oral administration, oral bioavailability was low in dogs (21%), but moderate in rats (58%) and monkeys (39%-78%). Based on 2-species allometric scaling from rats and monkeys, the terminal elimination half-life in humans is projected to be approximately 17 hours, and the oral bioavailability is projected to be approximately 40%. At a clinical dose of 12 mg QD, which is expected to provide plasma concentration exceeding IC_{50} (55 nM based on whole blood c-Myc inhibition) for 12 hours, the total steady-state plasma $AUC_{0\text{-}24}$ and C_{max} are estimated to be approximately 1.5 μM·h and 0.1 μM, respectively.

INCB057643 exhibits low in vitro permeability across Caco-2 monolayers and low aqueous solubility. *In vitro* transport studies indicate that INCB057643 is a substrate of both P-glycoprotein and breast cancer resistant protein efflux transporters, and neither efflux transporter was saturated up to 300 µM. INCB057643 has limited penetration across the rat blood-brain barrier (BBB), with a steady-state brain to plasma concentration ratio of 0.11. *In vitro* human protein binding of INCB057643 was low (unbound fraction of 49.1%), similar to that in preclinical species.

The interactions of INCB057643 with uptake and efflux transporters were evaluated using *in vitro* systems. Though INCB057643 is a moderate inhibitor of P glycoprotein, organic cation transporter (OCT)2, organic anion transporter (OAT)3, organic anion transporter polypeptide (OATP)1B3, and OATP1B1, no drug-drug interactions are expected based on the projected steady-state human plasma C_{max} and concentrations in the gut. Reaction phenotyping using recombinant human cytochrome P450s (CYPs) indicated that INCB057643 was primarily metabolized by CYP3A4/5, and therefore, it is possible that the PK of INCB057643 might be affected by coadministration of potent CYP3A4 inhibitors or inducers. INCB057643 is not an inhibitor of the major CYPs evaluated. The metabolism profiles of INCB057643 in rat, monkey, and human *in vitro* liver preparations were qualitatively similar. Analysis of plasma samples identified M3 (INCB070378) to be a major metabolite in rats and M2 (INCB057228) to be a major metabolite in monkeys *in vivo*. There was no evidence of a human-specific metabolite. Metabolite M2 (INCB057228) is an active metabolite with an IC_{50} of 29 nM (whole blood c-MYC inhibition) while M3 (INCB070378) was not active. The metabolites observed *in vitro* in human liver microsomes were also observed *in vivo* in preclinical species. No glutathione adducts were detected upon incubation of INCB057643 in human liver microsomes, suggesting that INCB057643 does not generate any reactive metabolites. Refer to the IB for additional details.

1.3. Overview of Standard-of-Care Agents Selected For Combination Therapies

1.3.1. Overview of Gemcitabine in Solid Tumors Including Ovarian Cancer

Gemcitabine is a nucleoside metabolic inhibitor that kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary, and it is currently approved in the United States and in the European Union to treat breast cancer, non–small-cell lung cancer (NSCLC), ovarian cancer, and pancreatic cancer either alone or in combination with other chemotherapy agents.

As a single agent, gemcitabine, as a salvage treatment for platinum refractory ovarian cancer, has been extensively evaluated at doses ranging from 800 to 1250 mg/m² administered as a 30-minute infusion on Days 1, 8, and 15 of a 28-day cycle. Using this dose and schedule, the most frequently occurring dose-limiting toxicities (DLTs) associated with gemcitabine treatment are hematologic, with neutropenia occurring more often than thrombocytopenia, are not cumulative, and can be managed with dose reductions and/or dose interruptions. Overall response rates varied from 14% to 22%, with an average of 16.5% across the all series with gemcitabine as salvage chemotherapy in mostly platinum-resistant or refractory ovarian cancer patients (some subjects had prior exposure to paclitaxel; Lorusso et al 2006). In a randomized Phase III study in subjects with platinum-resistant ovarian cancer (who progressed within

6 months of platinum-based therapy in the primary setting) comparing gemcitabine (1000 mg/m^2, Days 1 and 8 every 21 days) with Doxil® (liposomal doxorubicin; 50 mg/m^2, Day 1 every 28 days), median progression-free survival (mPFS) was 3.6 m versus 3.1 m, median overall survival (mOS) was 12.7m versus 13.5m, and objective response rate (ORR; in subjects with measurable disease) was 9.2% versus 11.7%, respectively. There was no statistically significant difference between the 2 treatments. The gemcitabine group experienced significantly more constipation, nausea/vomiting, fatigue, and neutropenia, and the doxorubicin group experienced significantly more hand-foot syndrome and mucositis (Mutch et al 2007). Single-agent gemcitabine has also been studied in lung cancer (Zatloukal et al 1998, Pérol et al 2012) and is one of the recommended single agents in the setting of treatment-refractory or resistant advanced or metastatic diseases (NCCN Guidelines).

1.3.2. Overview of Paclitaxel in Solid Tumors Including Ovarian Cancer

Paclitaxel is a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stabilization results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis, and as a result, induced cell death. It is currently approved in the United States and in the European Union to treat ovarian, metastatic breast cancer, locally advanced NSCLC and AIDS-related Kaposi's sarcoma.

Paclitaxel may be administered as single agent for patients who have Stage III/IV ovarian cancer with a recurrence within 6 months from initial or subsequent complete response from a platinum-containing chemotherapy [platinum-resistant] (Grabosch et al 2017, NCCN Guidelines). In a randomized Phase III study (AURELIA) comparing bevacizumab combined with chemotherapy versus chemotherapy alone (investigator's choice among pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan) in platinum-resistant recurrent ovarian cancer (excluding platinum-refractory disease), there was a statistically significant improvement in overall mPFS (6.7 m vs 3.4 m, hazard ratio = 0.48 [95% confidence interval (CI), 0.38 to 0.60]), unstratified log-rank $p < 0.001$), in mPFS of the paclitaxel cohort (Avastin® plus paclitaxel vs paclitaxel alone; 10.4 m vs 3.9 m, hazard ratio = 0.46), and in Response Evaluation Criteria in Solid Tumors (RECIST) ORR (27.3% vs 11.8% [$p = 0.001$]) and in ORR of the paclitaxel cohort (Avastin plus paclitaxel vs paclitaxel alone, 53.3% vs 30.2%) but no statistically significant improvement in mOS (16.6 m vs 13.3 m hazard ratio = 0.85 [95% CI, 0.66 to 1.08], $p < 0.174$; the study was not designed to formally compare overall survival [OS]). The only subgroup to approach a statistically significant improvement in OS was Avastin plus weekly paclitaxel in an exploratory analysis (unadjusted hazard ratio = 0.65 [95% CI, 0.42 to 1.02]; 22.4 m vs 13.2 m; Poveda et al 2015). Paclitaxel (175-200 mg/m^2 on Day 1 of every 3 weeks or 60-80 mg/m^2 on Day 1 of each week) has been studied in platinum-resistant ovarian cancer (Gynecologic Oncology Group et al 2006, Pignata et al 2015, Elit and Hirte 2013), breast (Siedman et al 1995, Perez et al 2001), and lung cancers (Lilenbaum et al 2005, Ceresoli et al 2004, Yasuda et al 2004), and is one of the recommended single agents in the setting of treatment-refractory or resistant advanced or metastatic diseases (NCCN Guidelines).

1.3.3. Overview of Rucaparib in Ovarian Cancer

Rucaparib is a PARP inhibitor indicated as a monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic)–associated advanced ovarian cancer who have been treated with 2 or more chemotherapies. It is currently approved in the United States under an accelerated approval based on ORR and duration of response (DOR) to treat advanced ovarian cancer with *BRCA* mutation.

In 2 multicenter, single-arm, open-label clinical studies in advanced ovarian cancer patients with *BRCA* mutation who had progressed after 2 or more prior chemotherapies, 106 subjects received rucaparib 600 mg orally BID. Investigator-assessed ORR was 54% (57/106; 95% CI, 44% to 64%). Median DOR for the 57 responders was 9.2 months (95% CI, 6.6 to 11.6 months). Objective response rate was 66% (52/79; 95% CI, 54% to 76%) in platinum-sensitive subjects, 25% (5/20; 95% CI, 9% to 49%) in platinum-resistant subjects, and 0% (0/7; 95% CI, 0% to 41%) in platinum-refractory subjects. Objective response rate was similar for subjects with a *BRCA1* gene mutation or a *BRCA2* gene mutation (Rubraca 2017).

Rucaparib has also been evaluated in platinum-sensitive ovarian cancer patients with BRCA wild type but genomic loss of heterozygosity (LOH) that may be a surrogate for homologous repair deficiency. Patients with *BRCA* wild type but LOH-high tumors showed improved PFS compared with *BRCA* wild type but LOH-low tumors suggesting potential clinical benefit to ovarian cancer patients with homologous repair deficiency in the absence of *BRCA* mutations. Rucaparib is also being investigated in the maintenance setting in patients with relapsed ovarian cancer with or without mutations in *BRCA* genes.

The recommended dose and schedule for rucaparib in patients with ovarian cancer *BRCA* mutation is 600 mg BID PO with or without food. This oral agent is prepared as 200, 250, and 300 mg tablets.

1.3.4. Overview of Abiraterone in Metastatic Castration-Resistant Prostate Cancer

Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor that inhibits 17 α-hydroxylase/C17, 20-lyase (CYP17). CYP17 is normally expressed in testicular, adrenal, and prostatic tissue and is required for androgen biosynthesis, and also expression in prostatic tumor tissue and metastatic lesions from castration-resistant prostate cancer (CRPC; Efstathiou et al 2012). CYP17 catalyzes 2 sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxyl derivatives by 17αhydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lysate activity. DHEA and androstenedione are androgens and are precursors of testosterone. CYP17A is a rational target to address persistent androgen synthesis and expression of prostate-specific antigen (PSA) and AR in CRPC following androgen deprivation therapy (ADT) (Page et al 2006, Mostaghel et al 2008). Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals, resulting in toxicities such as hypokalemia, hypertension, and fluid retention (Auchus et al 2014). It is currently approved in the United States and in the European Union to treat metastatic castrate resistant prostate cancer.

1.3.5. Overview of Azacitidine in Acute Myeloid Leukemia and Myelodysplastic Syndrome

Azacitidine is a nucleoside metabolic inhibitor that is approved in the United States and in the European Union for the treatment of patients with several different subtypes of myelodysplastic syndrome (MDS). 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). Azacitidine is recommended as a low-intensity induction therapy in AML, primarily in patients who are unfit for high- or intermediate-intensity regimens, especially in patients who are ≥ 60 years (NCCN Guidelines). In the AZA-AML-001 study (Dombret et al 2015), azacitidine (n = 241) was compared with conventional therapies (best supportive care, low-dose cytarabine [L-DAC], and standard induction therapy; n = 247) in subjects aged ≥ 65 years with newly diagnosed AML with > 30% bone marrow blasts. Median OS was improved (10.4 m vs 6.5 m, hazard ratio = 0.85, p = 0.10009) but did not reach statistical significance. Median OS did reach statistical significance (12.1 m vs 6.9 m, hazard ratio =0.76, p = 0.019), however, when the subjects were censored at the start of subsequent AML therapy by prespecified sensitivity analysis. Also, subjects with poor-risk cytogenetics (hazard ratio = 0.68) and with myelodysplasia-related changes (hazard ratio = 0.69) benefited significantly from azacitidine. Even though the study was not powered to compare azacitidine with individual conventional therapy, the OS of subjects treated with azacitidine or L-DAC (n = 154 vs n = 158, respectively) did not differ significantly, and comparable survival rates were also observed comparing azacitidine with standard induction therapy (n = 43 vs n = 44, respectively). Azacitidine is superior to best supportive care by post hoc analysis; azacitidine achieved a complete response (CR) of 19.5% vs 21.9% when compared with conventional therapies (CR/CRi was 27.8% vs 25.1%). The most common treatment-emergent adverse events (TEAEs) ≥ Grade 3 occurring in ≥ 20% of subjects in the azacitidine arm were febrile neutropenia, neutropenia, thrombocytopenia, pneumonia, and anemia. Although there has been limited investigation into the use of azacitidine in relapsed/refractory AML, Al-Ali et al (2012) reported a 10% ORR (including hematologic improvement) in subjects who were resistant to primary chemotherapy.

1.3.6. Overview of Ruxolitinib in Myelofibrosis

Ruxolitinib, a potent and selective inhibitor of JAKs 1 and 2, is approved in the United States and in the European Union for use in patients with intermediate- or high-risk MF, including primary myelofibrosis, post–polycythemia vera myelofibrosis, and post–essential thrombocythemia myelofibrosis. Registration studies showed improvement in spleen size, symptom burden, and OS with ruxolitinib use in this patient population (Cervantes et al 2013, Harrison et al 2012, Mesa et al 2013a, Mesa et al 2013b, Vannucchi et al 2015, Verstovsek et al 2012, Verstovsek et al 2013).

In the 2 pivotal Phase 3 studies of ruxolitinib in MF, INCB 18424-351 and CINC424A2352, 301 subjects had a median duration of exposure to ruxolitinib of 9.6 months (range, 2 to 17 months). The majority of subjects (55.8%) were treated for at least 9 months. The most frequently reported adverse events (AEs) were thrombocytopenia and anemia. Hematologic AEs (any CTCAE grade) included anemia (81.7%), thrombocytopenia (67.4%), and neutropenia (15.3%). Anemia, thrombocytopenia, and neutropenia are dose-related effects. The 3 most frequently reported nonhematologic AEs were bruising (18.6%), dizziness (14.0%), and

headache (12.6%). The 3 most frequently reported nonhematologic laboratory abnormalities were elevated alanine aminotransferase (ALT; 26.2%), elevated aspartate aminotransferase (AST; 18.6%), and hypercholesterolemia (16.6%). In Phase 3 clinical studies, discontinuation because of AEs, regardless of causality, was observed in 9.6% of subjects.

1.4. Study Rationale

INCB057643 is an oral BET protein inhibitor that is being developed for the treatment of advanced malignancies. The BET family of BRDs functions as transcriptional regulators binding to acetylation marks in chromatin at gene promoter and enhancer elements and recruiting transcription initiation and elongation complexes. In tumor cells, aberrant patterns of epigenetic marks including acetylation underlie abnormal transcriptional regulation of genes involved in cellular proliferation, survival, differentiation, and migration, thereby promoting an oncogenic program. Bromodomain and extra-terminal proteins are essential for the transcription of many of these genes; thus, inhibition of BET binding to chromatin may suppress oncogenic transcription in cancer cells. Suppression of these oncogenic factors has the potential to inhibit the growth of a variety of tumor cell types and may be efficacious in the treatment of advanced malignancies. Thus, study subjects with advanced cancer and no proven treatment options are candidates for this study to determine preliminary safety and efficacy of INCB057643. Furthermore, biochemical, tumor biomarker, and preclinical pharmacology studies have revealed that BET-inhibition may be useful in the treatment of a broad array of cancers, particularly those associated with activation of MYC, sonic hedgehog, and RAS pathways, among others. Preclinical data using INCB057643 as an inhibitor have demonstrated efficacy in several histologic subtypes with activation of these pathways, including lymphomas with c-Myc dysfunction, MM, AML, small cell lung cancer, high-grade serous ovarian cancer, and colorectal cancer (refer to the IB for additional details). Part 2 of the study will evaluate the safety, tolerability, and activity of INCB057643 administered as a single agent in a subset of solid tumors and hematologic malignancies that tend to be associated with these oncogenic profiles.

1.4.1. Rationale for Combining INCB57643 With Gemcitabine and Paclitaxel in Ovarian Cancer

Currently, ovarian cancer patients with Stage III/IV disease who have a recurrence < 6 months after first-line platinum-containing chemotherapy are considered platinum resistant and may be treated with second-line chemotherapy agents such as liposomal doxorubicin, gemcitabine, and paclitaxel, with or without Avastin (NCCN Guidelines). Approximately 40% of patients are currently not being treated/ineligible to receive Avastin in this setting. After a finite number of recurrences, most patients, including those with initial platinum-sensitive diseases, will develop platinum-resistant disease with a poor prognosis and die as a result of their disease. There is an urgent unmet medical need to identify additional agents such as INCB057643 to either enhance or create a synergistic effect with SOC agents such as gemcitabine and paclitaxel in platinum-resistant ovarian cancer. [redacted]

1.4.2. Rationale for Combining INCB57643 With Rucaparib in Ovarian Cancer

Poly (adenosine diphosphate-ribose) polymerase inhibitors, including rucaparib and olaparib, have been approved as monotherapy for treatment of advanced ovarian cancer with *BRCA1/2* mutations (Lord and Ashworth 2017). Poly (adenosine diphosphate-ribose) polymerase proteins are involved in many aspects of gene transcription and DNA repair, including base excision repair; inhibition of PARP enzymatic activity by small molecules results in the generation of double-stranded DNA breaks that are normally repaired by the homologous recombination pathway (Konstantinopoulos et al 2015). Cells with homologous recombination deficiency, such as through *BRCA1/2* inactivation, are unable to repair these lesions and undergo cell death in the presence of a PARP inhibitor. Therefore, PARP inhibitors exhibit synthetic lethality in homologous recombination–deficient tumors.

In high-grade serous ovarian cancer, approximately 50% of tumors have genetic defects in homologous recombination. However, a large fraction of patients remain homologous recombination–proficient, and treatment-emergent mechanisms of resistance to PARP inhibitors include reversion of *BRCA1/2* mutations to restore homologous recombination function (Konstantinopoulos et al 2015). Therefore, strategies to block homologous recombination function could sensitize de novo or acquired resistant tumors to PARP inhibition. Bromodomain and extra-terminal inhibitors were found to synergize with PARP inhibitors in an unbiased chemical library screen (Yang et al 2017). Ribonucleic acid sequencing analysis revealed that the BET inhibitor decreased the expression of *BRCA1* and *RAD51*, 2 essential genes in the homologous recombination pathway. Functional studies showed that the BET inhibition decreased homologous recombination–mediated repair of double-stranded DNA breaks upon treatment of homologous recombination–proficient cells with a PARP inhibitor, resulting in suppressed colony formation *in vitro*. The combination of BET inhibitor and PARP inhibitor exhibited greater tumor growth inhibition than either single agent in xenograft models of homologous recombination–proficient ovarian and breast cancers. Therefore, BET inhibition creates a BRCAness phenotype in homologous recombination–proficient cancer cells and sensitizes them to PARP inhibition. Independent synergy between the Incyte BET inhibitor INCB054329 and olaparib was demonstrated in homologous recombination–proficient ovarian cancer cell lines and in a xenograft model of SKOV3 ovarian cancer tumors that provides further support for this mechanism (Wilson et al 2017). In addition, the combination of BET inhibitor and PARP inhibitor also demonstrated synergy in tumor growth inhibition in homologous recombination–deficient ovarian cancer models (Yang et al 2017).

1.4.3. Rationale for Combining INCB57643 With Abiraterone in Castration-Resistant Prostate Cancer

The clinical importance of ongoing AR pathway activity in CRPC progression is reflected in the rising serum PSA levels in patients with CRPC following ADT and is confirmed by clinical responses to treatment strategies that target residual AR axis activity in CRPC with next generation anti-androgen therapies including abiraterone and enzalutamide (Ryan et al 2015). However, not all CRPC patients respond to abiraterone or enzalutamide (20%-30% of patients are unresponsive to both agents up front), and most responders develop resistance with a widely variable DOR (20%-30% have transient responses of 2-3 months). Several resistance mechanisms have been hypothesized, including activated AR signaling axis, such as AR splice variants, up-regulation of CYP17A1, up-regulation of full-length AR, AR activation by

noncanonical ligands, treatment-emergent neuroendocrine differentiation/small-cell phenotype often associated with the N-MYC amplification, and impaired DNA damage repair pathway/*BRCA2* and ATM mutations (Giacinti et al 2014, Bubley and Balk 2017). Several of these resistant mechanisms have been show to provide cross-resistance, such as up-regulation of CYP17, up-regulation of AR, and de novo or treatment-emergent AR splice variants (Antonarakis et al 2014). As a result, the responses to the second-line treatment of CRPC with abiraterone following progression on first-line enzalutamide, or vice versa, were usually poor (Chandrasekar et al 2015). Bromodomain and extra-terminal inhibitors, including INCB057643, have been shown to inhibit AR signaling pathways through multiple mechanisms and are active in enzalutamide- and abiraterone-resistant models (Section 1.1). Therefore, it is hypothesized that INCB057643 in combination with abiraterone will overcome and/or prevent enzalutamide- and abiraterone-induced resistance mechanisms.

1.4.4. Rationale for Combining INCB57643 With Ruxolitinib in Myelofibrosis

Despite statistically significant improvements in signs and symptoms of MF and OS rates, ruxolitinib monotherapy, when compared with either placebo or best available therapy demonstrated in the registration studies, fails to provide adequate and/or sustained response for some subjects. A subgroup analysis of the Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment I (COMFORT-I) study did not identify subgroups (age, MF subtype, International Prognostic Scoring System risk group, baseline ECOG score, baseline platelet or hemoglobin level, baseline spleen volume quartile, baseline symptom burden quartile, or presence/absence of V617F mutation) that benefitted from ruxolitinib therapy (Verstovsek et al 2013); however, additional systemic and genetic factors may influence the response magnitude and duration in an individual patient. It is possible that for some patients, declining hemoglobin or platelet counts associated with ruxolitinib use preclude maintenance at optimal ruxolitinib dosages. Alternatively, some patients may have increases in inflammatory pathway signaling that are not JAK-mediated as primary drivers for their disease. Therefore, new approaches such as combination therapy are needed to provide adequate and/or sustained responses for MF patients who do not achieve such with ruxolitinib monotherapy. Bromodomain and extra-terminal inhibitors including INCB057643 have been shown to inhibit the JAK/STAT pathway and the inflammatory pathway (see Section 1.1). It is hypothesized that INCB057643 in combination with ruxolitinib will enhance both disease and symptom control compared with ruxolitinib alone.

1.4.5. Rationale for Combining INCB57643 With Azacitidine in Acute Myeloid Leukemia/High-Risk Myelodysplastic Syndrome

For relapsed or refractory AML and HR-MDS, azacitidine is often used as a less aggressive salvage therapy option. For newly diagnosed AML in patients aged ≥ 65 years old, azacitidine is recommended as a low-intensity induction therapy, primarily in those who are unfit for high- or intermediate-intensity regimens (see Section 1.3.5, NCCN Guidelines). However, in both disease populations, the clinical responses (CR/CRi) and their DORs were limited with the CR + CRi rate < 30% and mOS < 10 m, and, as such, new approaches are urgently needed. Bromodomain and extra-terminal inhibitors including INCB057643 have been shown to be active in de novo and secondary AML and MDS models (see Section 1.1). It is hypothesized

that the combination of INCB57643 with azacitidine will be able to achieve better clinical efficacy in order to increase clinical remission rate and duration and OS.

1.5. INCB057643 Safety and Potential Risks

1.5.1. Preclinical Safety and Risks

The toxicity of INCB057643 was evaluated in 28-day and 3-month GLP studies in Sprague Dawley rats and cynomolgus monkeys. Doses for the pivotal GLP studies were selected based on results of range-finding studies and prior experience with other BET inhibitors.

In rat studies, target organs of toxicity based on microscopic findings included lymphoid organs, bone/bone marrow, stomach/gastrointestinal (GI) tract, lungs, and reproductive tract. All findings were reversible. All of these findings were considered to be related to the pharmacologic activity of INCB057643 (ie, there were no off-target toxicities).

The 28-day monkey study did not result in any adverse effects at any dose level (2.5 mg/kg per day was the highest dose tested).

In the 3-month monkey study, dose levels of 1, 2.5, and 5 mg/kg per day were evaluated. Dose levels of 2.5 and 5 mg/kg per day were not tolerated, and these groups were euthanized early (approximately Days 40 and 20, respectively). Several animals in these groups exhibited signs of hemorrhage (bruising, hematoma, dark red areas throughout GI tract at necropsy). Histopathology findings in these groups were similar, including mucosal atrophy, degeneration/regeneration, inflammation, and hemorrhage in the GI tract; minimal to moderate cardiac myopathy characterized by single to multiple foci of myocardiocyte atrophy/degeneration in the heart; minimal to severe decrease in bone marrow cellularity in the bone marrow; lymphoid depletion in the thymus; and atrophy, degeneration and regeneration in the pancreas. Hypoactivity, liquid feces, and dehydration were observed clinically in some of the animals, along with altered electrolytes in calcium, chloride, phosphorous, potassium, and/or sodium. Thrombocytopenia and anemia were also observed in some animals. Mild cardiac myopathy was observed in a single animal administered 1 mg/kg per day. Based on steady state exposure data from the 28-day toxicology study in cynomolgus monkeys, the exposure at 2.5 mg/kg per day in monkeys is expected to be equivalent to 1.1-fold of the human exposure at 12 mg QD observed in the INCB 57643-101 study. This finding of cardiac myopathy met the criteria for an Expedited Safety Report, as it was unexpected, related to the drug, and presented a potential risk to the subjects in the INCB 57643-101 study, which was submitted to regulatory agency on 23 MAR 2018.

Several findings in the toxicity studies were anticipated based on the pharmacology of BET inhibition. Degeneration, erosion, and/or ulceration of the mucosal epithelium of the stomach observed in rats and the GI tract of monkeys are consistent with anticipated effects of BRD4 inhibition in the GI tract. Exploratory studies in rats conducted using structurally similar and structurally distinct BET protein inhibitors demonstrate that all of these compounds produce similar GI toxicity, the onset of which occurs at exposures expected to produce significant pharmacologic activity. The GI findings were reversible. Effects on the bone, bone marrow, and lymphoid organs are also expected based on the mechanism of action of INCB057643 and were reversible in the 28-day rat study. Due to early euthanization of all the monkeys treated at 2.5 and 5 mg/kg per day in the 3-month monkey study, the reversibility of the toxicities observed

is largely unknown. However, based on its severity, cardiac histopathologic findings would not be expected to be reversible.

The PK of INCB057643 was characterized in rats, dogs, and monkeys. The urinary excretion of INCB057643 was determined to be 12.5% of dose in monkeys, 17.6% in rats, and 26.1% in dogs. Further, *in vitro,* and *in vivo* metabolism studies in animals indicate generation of major and minor metabolites. These data indicate that renal clearance is not the major route of clearance for INCB057643 and that metabolism is likely the predominant clearance pathway. The clearance mechanism of the active metabolite, INCB057228, is less clear; however, exposure of this metabolite in patients is only about 10% to 15% of the parent compound.

Enrollment of subjects with mild to moderate organ impairment (≤ Grade 2 creatinine clearance) in the carefully monitored Phase 1 setting would allow us to better understand the impact of such organ dysfunction on the disposition of INCB057643 and in turn would inform the inclusion/exclusion criteria for Phase 2 studies.

Subjects in enrolling this study will be informed of the potential risks identified in animal studies. Subjects will be closely monitored for any signs of GI symptoms and will have hematologic parameters, as well as blood chemistries, closely monitored during study participation. Subjects will also be regularly monitored by echocardiogram or MUGA, including ejection fraction change, and cardiac troponin testing. The dose of INCB057643 may be interrupted or adjusted in subjects experiencing AEs. Effects on fertility and fetal development have not been evaluated. Men should avoid fathering a child and women of childbearing potential should take appropriate contraceptive measures from the time of screening through follow-up. Refer to the IB for additional details.

1.5.2. Potential Risks of Gemcitabine

Risks associated with use of gemcitabine include myelosuppression, which is the principal DLT. Gemcitabine can suppress bone marrow function as manifested by leukopenia, neutropenia, thrombocytopenia, and anemia. Subjects should be monitored for myelosuppression during therapy. Subjects may also experience pulmonary toxicity and respiratory failure, hepatic toxicity, and capillary leak syndrome. The most common adverse reactions as monotherapy are nausea; vomiting; anemia; increased ALT, AST, and alkaline phosphatase (ALP); neutropenia; leukopenia; proteinuria; fever; hematuria; rash; thrombocytopenia; and dyspnea. A complete discussion of risks associated with gemcitabine can be found in the United States Prescribing Information (USPI; Gemzar 2017) or in the Summary of Product Characteristics (SmPC; Gemzar 2008).

1.5.3. Potential Risks of Paclitaxel

Risks associated with the use of paclitaxel include myelosuppression, which is the principal DLT. Paclitaxel can suppress bone marrow function as manifested by neutropenia, leukopenia, thrombocytopenia, and anemia. Subjects should be monitored for myelosuppression during therapy. Subjects may also experience infections, bleeding, hypersensitivity reactions, bradycardia, hypotension, abnormal electrocardiograms (ECGs), peripheral neuropathy, myalgia and arthralgia, nausea and vomiting, diarrhea, mucositis, alopecia, bilirubin elevation, alkaline phosphate increase, AST increase, and injection site reaction. A complete discussion of risks

associated with paclitaxel can be found in the USPI (Taxol 2011) or in the SmPC (Abraxane 2016).

1.5.4. Potential Risks of Rucaparib

There are risks associated with the use of rucaparib, including warnings and precautions for MDS/AML. Monitor subjects for hematological toxicities including anemia, thrombocytopenia, neutropenia, and lymphopenia. The most common AEs (≥ 20%) include nausea, fatigue (including asthenia), vomiting, anemia, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhea, thrombocytopenia, and dyspnea. The most common laboratory abnormalities (≥ 35%) are increase in creatinine, increase in ALT, increase in AST, decrease in hemoglobin, decrease in lymphocytes, increase in cholesterol, decrease in platelets, and decrease in absolute neutrophil count (ANC). Fetal harm can also occur in patients taking rucaparib; advise females of the potential reproductive risk to a fetus and to use effective contraception. A complete discussion of risks associated with rucaparib can be found in the USPI (Rubraca 2017).

1.5.5. Potentials Risks of Abiraterone

Risks associated with the use of abiraterone include mineralocorticoid excess, adrenocortical insufficiency, and hepatotoxicity. Abiraterone should be used with caution in subjects who have a history of cardiovascular disease. Subjects should be monitored for hypokalemia, hypertension, and liver function abnormalities. The most common AEs as monotherapy are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection, and contusions. The most common laboratory abnormalities are anemia, elevated alkaline phosphate, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT, and hypokalemia. A complete discussion of risks associated with paclitaxel can be found in the USPI (Zytiga 2017a) or in the SmPC (Zytiga 2017b).

1.5.6. Potential Risks of Ruxolitinib

Risks associated with the use of ruxolitinib include thrombocytopenia, which is the principal DLT. Subjects should be monitored for thrombocytopenia. The most common AEs as monotherapy are thrombocytopenia, anemia, bruising, dizziness and headache, elevated ALT, elevated AST, and hypercholesterolemia. A complete discussion of risks associated with ruxolitinib can be found in the USPI (Jakafi 2016) or in the SmPC (Jakavi 2017).

1.5.7. Potential Risks of Azacitidine

Risks associated with the use of azacitidine include anemia, neutropenia, and thrombocytopenia which are the principal DLTs. The most common adverse reactions > 30% by the SC route are nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia and ecchymosis. The most common adverse reactions by the IV route are petechiae, rigors, weakness, and hypokalemia. A complete discussion of risks associated with azacitidine can be found in the USPI (Vidaza 2016) or in the SmPC (Vidaza 2017).

1.5.8. Potential Risks of Combination Therapy

INCB057643 has not been combined with gemcitabine, paclitaxel, rucaparib, abiraterone, ruxolitinib, or azacitidine previously in the clinical setting. The effects of these combinations are being assessed in this protocol. As described above, the most common AEs associated with these SOC agents are neutropenia, anemia, thrombocytopenia, nausea, vomiting, diarrhea, and liver function abnormalities. The most common AEs associated with INCB057643 have been thrombocytopenia and GI AEs (see Section 1.6.2). Adverse events will be monitored to identify occurrences of new safety signals or potentiation of any SOC agents and INCB05764-related side effects.

1.6. Clinical Experience With INCB057643 in Study INCB 57643-101

1.6.1. Clinical Pharmacokinetics and Pharmacodynamics

Preliminary PK data are available for 42 subjects who have received INCB057643 8 mg QD, 12 mg QD, or 16 mg QD in Study INCB 57643-101. With multiple-dose administration, INCB057643 attained peak plasma concentrations with a median T_{max} of 1 to 2 hours. Subsequently, INCB057643 plasma concentrations declined in a monophasic manner with a mean terminal phase half-life ranging from 8.31 to 15.3 hours. M2 (INCB057228), a major and active metabolite, achieved peak plasma concentrations with a median T_{max} of 2 to 4 hours. INCB057228 plasma concentrations declined in a monophasic manner with a mean terminal phase half-life ranging from 12.3 to 14.4 hours. An approximately linear relationship was observed for INCB057643 exposures (C_{max} and AUC) over the dose range studied (Table 1). No significant food effect on PK has been observed based on preliminary data (Table 2).

Table 1: INCB057643 (Parent) and INCB057228 (M2) Steady-State (Cycle 1 Day 8) Pharmacokinetic Parameters

Analyte	Treatment Group	Dose (mg)	N	C_{max} (nM)	T_{max} (h)	C_{min} (nM)	$AUC_{0-\tau}$ (nM·h)	CL/F (L/h)	V_z/F (L)	$t_{½}$ (h)
INCB057643 (Parent)	Part 1/TGA	8	4	224 ± 149 (185)	1.0 (1.0, 4.0)	35.7 ± 33.8 (26.6)	2060 ± 1240 (1800)	12.1 ± 6.89 (10.7)	156 ± 55.3 (149)	10.3 ± 4.59 (9.65)
	Part 1/TGA	12	3	233 ± 24.4 (232)	2.0 (2.0, 4.0)	49.1 ± 8.17 (48.6)	2860 ± 321 (2850)	10.2 ± 1.1 (10.2)	144 ± 23.6 (142)	9.47 ± 1.1 (9.71)
	Part 1/TGA	16	7	340 ± 165 (310)	2.0 (2.0, 4.0)	101 ± 87.4 (64.0)	4330 ± 2860 (3620)	12.6 ± 7.48 (10.7)	212 ± 73.4 (198)	15.3 ± 9.67 (12.9)
	Part 2/TGA	12	22	295 ± 104 (279)	2.0 (1.0, 6.0)	39.9 ± 25.7 (33.0)	2820 ± 1190 (2620)	11.8 ± 4.29 (11.0)	138 ± 44.7 (129)	8.31 ± 2.56 (7.95)
	Part 1/TGB	8	6	178 ± 63.8 (167)	1.0 (0.5, 2.0)	28.4 ± 13.9 (24.4)	1850 ± 471 (1800)	11.1 ± 3.4 (10.7)	134 ± 63.7 (121)	8.57 ± 2.62 (8.12)
INCB057228 (M2)	Part 1/TGA	8	4	17.7 ± 8.06 (16.2)	2.0 (2.0, 6.0)	5.46 ± 4.59 (4.36)	250 ± 137 (225)	94.5 ± 45.9 (85.8)	1390 ± 466 (1330)	14.4 ± 7.42 (13.1)
	Part 1/TGA	12	3	19.2 ± 10.5 (16.7)	2.0 (2.0, 8.0)	7.32 ± 4.84 (5.83)	314 ± 192 (261)	141 ± 123 (111)	4720, 1290	11.6, 14.7
	Part 1/TGA	16	6	52.1 ± 30.2 (44.2)	4.0 (2.0, 6.0)	15.1 ± 9.95 (12.7)	717 ± 351 (643)	67.2 ± 35.8 (60)	1290 ± 927 (100)	14.1 ± 5.39 (13.3)
	Part 2/TGA	12	22	37.3 ± 22.0 (32.4)	2.0 (1.0, 8.0)	9.15 ± 6.17 (7.63)	507 ± 261 (448)	73.6 ± 40.4 (64.6)	1360 ± 1100 (1080)	12.3 ± 5.26 (11.3)
	Part 1/TGB	8	6	25.9 ± 12.1 (22.6)	2.0 (0, 4.0)	9.22 ± 5.22 (7.70)	390 ± 171 (355)	60.8 ± 33.6 (54.4)	849 ± 228 (823)	13.5 ± 5.67 (12.3)

Note: All values are presented as mean ± SD (geometric mean) with the exception of T_{max}, which is presented as median (minimum, maximum).
Note: The predose PK samples on Cycle 1 Day 8 were imputed as the 24-hour trough samples.

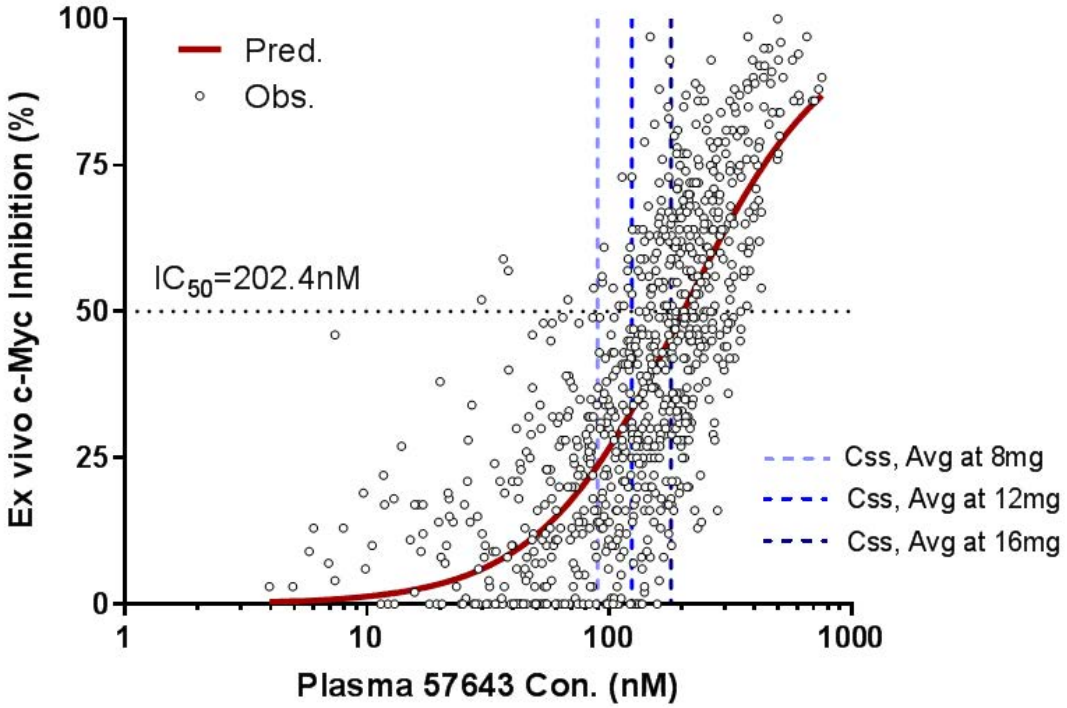
Table 2: The Effect of a High-Fat Meal on the Pharmacokinetics of INCB057643 (12 mg) and INCB057228 (M2)

Analyte	N	Treatment	C_{max} (nM)	T_{max} (h)	AUC_{τ} (h·nM)	CL/F (L/h)	V/F (L)
57643	11	Fasted (C1D8)[a]	281 ± 87.4 (268)	2.0 (2.0, 6.0)	2980 ± 1030 (2820)	10.9 ± 4.13 (10.3)	142 ± 44.5 (136)
	12	Fed (C2D1)	253 ± 75.8 (242)	6.0 (4.0, 24.0)	3500 ± 1220 (3300)	9.33 ± 3.48 (8.77)	148 ± 35.5 (145)
57228	11	Fasted (C1D8)	35.2 ± 14.2 (32.3)	4.0 (2.0, 8.0)	519 ± 243 (470)	–	–
	12	Fed (C2D1)	38.5 ± 28.8 (30.4)	8.0 (4.0, 24.0)	630 ± 445 (511)	–	–
Geometric mean ratio (reference = fasted)							
57643			0.89 (0.78, 1.01)		1.13 (0.99, 1.29)		
57228			0.95 (0.74, 1.22)		1.07 (0.86, 1.33)		

C1D8 = Cycle 1 Day 8; C2D1 = Cycle 2 Day 1.
Note: All values are presented as mean ± SD (geometric mean) with the exception of T_{max}, which is presented as median (minimum, maximum).
[a] The predose PK samples on Cycle 1 Day 8 were imputed as the 24-hour trough samples.

Pharmacodynamic analysis was performed using an ex vivo assay measuring protein levels of c-MYC, a BRD4 target gene, in KMS12BM cells spiked into subject plasma. In preliminary PD analysis after oral administration of 8 mg, 12 mg, and 16 mg, INCB057643 demonstrated inhibition of total c-Myc with maximal inhibition occurring between 1 and 4 hours after drug administration. The average c-Myc inhibition at steady state (Day 8, from predose to 8 hours) was 30%, 44%, and 65% for doses of 8 mg (n = 11), 12 mg (n = 51), and 16 mg (n = 7), respectively. Maximum peak inhibition of total c-Myc ranged from approximately 16% to 77% at 8 mg, 20% to 92% at 12 mg, and 61% to 97% at 16 mg. Inhibition of c-Myc was reduced to < 10% at trough (Cycle 1 Day 8 predose) for subjects receiving INCB057643 8 mg and 12 mg and approximately 30% for subjects receiving INCB057643 16 mg. A composite PK-PD curve was plotted for 67 subjects, and an IC_{50} value of 202.4 nM was determined by nonlinear regression curve fitting (see Figure 1).

Figure 1: Composite PK-PD Curve for Subjects in Study INCB 57643-101 (N = 67)



1.6.2. Clinical Trial Experience

1.6.2.1. Dose-Escalation and Expansion, Safety, and Tolerability Study of INCB057643 in Subjects With Advanced Malignancies

As of the data cutoff date 19 JAN 2018, 113 subjects with advanced malignancies have received at least 1 dose of INCB057643 on Study INCB 57643-101: 17 subjects in Part 1/TGA, 12 subjects in Part 1/TGB, 1 subject in Part 1/TGC, 80 subjects in Part 2/TGA, 1 subject in Part 2/TGB, and 2 subjects in Part 3/TGF. INCB057643 8 mg QD, 12 mg QD, or 16 mg QD has been administered as monotherapy (111 subjects) in Parts 1 and 2. INCB057643 8 mg QD has been administered in combination with azacitidine (2 subjects) in Part 3. No subjects have been enrolled in Part 4. Part 4 will not be opened for enrollment.

As of MAR 2018, no further subjects are being enrolled in all the cohorts due to a less favorable benefit/risk assessment based on emerging data, mainly the histopathological finding of cardiac myopathy observed in the preclinical 3-month toxicology study in monkeys (Section 1.5.1).

1.6.2.1.1. Part 1 Monotherapy Dose Escalation

In Part 1/TGA, doses of 8 mg QD, 12 mg QD, and 16 mg QD were evaluated. All 17 subjects (100%) in the clinical database reported at least 1 TEAE. Frequently reported TEAEs (≥ 25.0% incidence) included fatigue, nausea, decreased appetite, diarrhea, and hyperglycemia (see Table 3). Serious AEs occurred in 8 subjects (47.1%); the majority of the SAEs were reported at the nontolerated dose of 16 mg QD. One subject receiving 16 mg QD had an SAE of Grade 3 increased INR that was resolved with interruption of study drug and supportive care, which was deemed a DLT and considered by the investigator to be related to study treatment; the subject

was taking warfarin at the time of the event. The SAEs reported in the 8 mg QD and 12 mg QD groups were performance status decreased, sepsis, and tumor pain (8 mg QD) and hepatic failure (12 mg QD). Two fatal SAEs occurred in Part 1/TGA, including hepatic failure (12 mg QD) and pneumonia (16 mg QD), both deemed not related to the study drug by the investigators. Four subjects (23.5%) in Part 1/TGA discontinued INCB057643 treatment because of TEAEs: 3 subjects at 16 mg QD (abdominal pain upper and confusional state, hyperglycemia, and INR increased, respectively) and 1 subject at 8 mg QD (performance status decreased). There were no TEAEs leading to discontinuation at 12 mg QD.

Two subjects (11.8%) in Part 1/TGA (at 8 mg QD and 16 mg QD, respectively) reported TEAEs of herpes zoster (Grade 2). Both events were resolved with SOC measures and without study drug interruption.

The 16 mg QD dose in Part 1/TGA was deemed not tolerated due to DLT and other TEAEs leading to dose interruption, reduction, and termination. The 12 mg QD dose was selected as MTD and RP2D for further evaluation in Part 2/TGA monotherapy expansion.

Table 3: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 2 Subjects in Study INCB 57643-101 Part 1 Treatment Group A by MedDRA Preferred Term in Decreasing Order of Frequency (Safety Evaluable Population)

MedDRA Preferred Term, n (%)	8 mg QD (N = 4)	12 mg QD (N = 5)	16 mg QD (N = 8)	Total (N = 17)
Fatigue	2 (50.0)	4 (80.0)	4 (50.0)	10 (58.8)
Nausea	3 (75.0)	4 (80.0)	3 (37.5)	10 (58.8)
Decreased appetite	2 (50.0)	2 (40.0)	3 (37.5)	7 (41.2)
Diarrhoea	1 (25.0)	2 (40.0)	3 (37.5)	6 (35.3)
Hyperglycaemia	2 (50.0)	0	4 (50.0)	6 (35.3)
Abdominal pain	0	2 (40.0)	2 (25.0)	4 (23.5)
Anemia	0	1 (20.0)	3 (37.5)	4 (23.5)
Thrombocytopenia/platelet count decreased[a]	1 (25.0)	0	3 (37.5)	4 (23.5)
Urinary tract infection	3 (75.0)	0	1 (12.5)	4 (23.5)
Vomiting	2 (50.0)	2 (40.0)	0	4 (23.5)
Weight decreased	2 (50.0)	1 (20.0)	1 (12.5)	4 (23.5)
Back pain	1 (25.0)	1 (20.0)	1 (12.5)	3 (17.6)
Constipation	0	2 (40.0)	1 (12.5)	3 (17.6)
Dizziness	1 (25.0)	1 (20.0)	1 (12.5)	3 (17.6)
Dry mouth	1 (25.0)	1 (20.0)	1 (12.5)	3 (17.6)
Dysgeusia	0	1 (20.0)	2 (25.0)	3 (17.6)
Hypertension	0	1 (20.0)	2 (25.0)	3 (17.6)
Pruritus	1 (25.0)	1 (20.0)	1 (12.5)	3 (17.6)

Table 3: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 2 Subjects in Study INCB 57643-101 Part 1 Treatment Group A by MedDRA Preferred Term in Decreasing Order of Frequency (Safety Evaluable Population) (Continued)

MedDRA Preferred Term, n (%)	8 mg QD (N = 4)	12 mg QD (N = 5)	16 mg QD (N = 8)	Total (N = 17)
Cough	1 (25.0)	1 (20.0)	0	2 (11.8)
Depression	2 (50.0)	0	0	2 (11.8)
Herpes zoster	1 (25.0)	0	1 (12.5)	2 (11.8)
Influenza like illness	1 (25.0)	0	1 (12.5)	2 (11.8)
Muscle spasms	1 (25.0)	0	1 (12.5)	2 (11.8)
Performance status decreased	1 (25.0)	0	1 (12.5)	2 (11.8)

[a] Subjects for whom both preferred terms were reported are counted only once. Overall, platelet count decreased was reported for 3 subjects, and thrombocytopenia was reported for 1 subject.

In Part 1/TGB, doses of 8 mg QD and 12 mg QD were evaluated. All 12 subjects (100%) in the clinical database reported at least 1 TEAE (see Table 4). The most frequently reported TEAEs (≥ 30% of subjects) in this group were anemia, thrombocytopenia/platelet count decreased, diarrhea, epistaxis, fatigue, decreased appetite, dyspnea, and febrile neutropenia. In the clinical database, SAEs were reported for 8 subjects (66.7%) in Part 1/TGB; SAEs reported in more than 1 subject included febrile neutropenia (3 subjects, 25.0%), acute kidney injury (2 subjects, 16.7%), and respiratory failure (2 subjects, 16.7%). Fatal TEAEs were reported for 3 subjects (25.0%) in Part 1/TGB and included anemia and thrombocytopenia, sepsis, and acute kidney injury, respectively, all deemed not related to study drug by the investigators. Two subjects in Part 1/TGB discontinued INCB057643 treatment because of TEAEs (anemia and thrombocytopenia and nausea, respectively).

Coagulation-related events were reported for 2 subjects in Part 1/TGB. Events of increased INR (G1) and aPTT prolonged (G1) were reported for 1 subject at 12 mg QD, and aPTT prolonged (G2) was reported for 1 subject at 8 mg QD.

The dose of 12 mg QD was selected as MTD and RP2D in Part 1/TGB for further evaluation in Part 2/TGB.

Table 4: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 2 Subjects in Study INCB 57643-101 Part 1 Treatment Group B by MedDRA Preferred Term in Decreasing Order of Frequency (Safety Evaluable Population)

MedDRA Preferred Term, n (%)	8 mg QD (N = 7)	12 mg QD (N = 5)	Total (N = 12)
Anaemia	5 (71.4)	3 (60.0)	8 (66.7)
Thrombocytopenia/platelet count decreased[a]	5 (71.4)	3 (60.0)	8 (66.7)
Diarrhoea	4 (57.1)	1 (20.0)	5 (41.7)
Epistaxis	2 (28.6)	3 (60.0)	5 (41.7)
Fatigue	3 (42.9)	2 (40.0)	5 (41.7)
Decreased appetite	3 (42.9)	1 (20.0)	4 (33.3)
Dyspnoea	2 (28.6)	2 (40.0)	4 (33.3)
Febrile neutropenia	2 (28.6)	2 (40.0)	4 (33.3)
Acute kidney injury	3 (42.9)	0	3 (25.0)
Fall	2 (28.6)	1 (20.0)	3 (25.0)
Lung infection	2 (28.6)	1 (20.0)	3 (25.0)
Nausea	3 (42.9)	0	3 (25.0)
Oropharyngeal pain	2 (28.6)	1 (20.0)	3 (25.0)
Stomatitis	2 (28.6)	1 (20.0)	3 (25.0)
Vomiting	3 (42.9)	0	3 (25.0)
Activated partial thromboplastin time prolonged	1 (14.3)	1 (20.0)	2 (16.7)
Atrial fibrillation	1 (14.3)	1 (20.0)	2 (16.7)
Cough	0	2 (40.0)	2 (16.7)
Dehydration	2 (28.6)	0	2 (16.7)
Dry mouth	2 (28.6)	0	2 (16.7)
Dysgeusia	1 (14.3)	1 (20.0)	2 (16.7)
Hypotension	1 (14.3)	1 (20.0)	2 (16.7)
Hypoxia	2 (28.6)	0	2 (16.7)
Non-cardiac chest pain	1 (14.3)	1 (20.0)	2 (16.7)
Oral pain	2 (28.6)	0	2 (16.7)
Pyrexia	2 (28.6)	0	2 (16.7)
Respiratory failure	2 (28.6)	0	2 (16.7)
Sinus tachycardia	0	2 (40.0)	2 (16.7)
White blood cell count decreased	0	2 (40.0)	2 (16.7)

[a] Subjects for whom both preferred terms were reported are counted only once. Overall, platelet count decreased was reported for 5 subjects, and thrombocytopenia was reported for 3 subjects.

In Part 1/TGC, TEAEs reported for the single enrolled subject included cough, fatigue, and oropharyngeal pain; fatal SAEs while on study drug of sepsis, septic shock, and organ failure were also reported and deemed not related to study drug by the investigators.

1.6.2.1.2. Part 2 Monotherapy Dose Expansion

In Part 2/TGA, 77 of the 80 subjects (96.3%) in the clinical database reported at least 1 TEAE (see Table 5). The most frequently reported TEAEs (≥ 25% of subjects) included nausea, fatigue, thrombocytopenia/platelet count decreased, decreased appetite, and vomiting. In the

clinical database, SAEs were reported for 33 subjects (41.3%) in Part 2/TGA. Serious AEs reported for more than 1 subject included thrombocytopenia/platelet count decreased (6 subjects, 7.5%), respiratory failure (4 subjects, 5.0%); abdominal pain and sepsis (3 subjects each, 3.8%); and anemia, hypotension, muscular weakness, and urosepsis (2 subjects each, 2.5%). Fatal TEAEs were reported for 7 subjects (8.8%) in Part 2/TGA and included respiratory failure (4 subjects) and cardiac arrest, cardiac failure, pyuria, sepsis, liver function test increased, fluid overload, depressed level of consciousness, death, and disease progression (reported for 1 subject each), all of which were deemed not related to study drug by the investigators. Eleven subjects in Part 2/TGA discontinued INCB057643 treatment because of TEAEs (ie, anemia, thrombocytopenia/platelet count decreased, nausea, disease progression, fatigue, hepatic failure, hyperbilirubinemia, sepsis, weight decreased, spinal cord infarction, and dyspnea).

In Part 2/TGA, 5 subjects had increased INR (1 Grade 3 and reported as an SAE and 4 ≤ Grade 2). The subject who had the Grade 3 SAE of increased INR was taking concomitant warfarin. The 4 subjects who had ≤ Grade 2 increased INR were on alternative anticoagulant therapies. Two additional subjects reported aPTT prolonged (Grade 2), and 1 additional subject reported PT prolonged (Grade 2) with an increased INR (Grade 2).

Five subjects in Part 2/TGA (12 mg QD) reported TEAEs of herpes zoster (≤ Grade 2), 4 of which were resolved with SOC measures. The other was considered "not recovered/not resolved" at the time of death due to disease progression.

Table 5: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 10% of Subjects in Study INCB 57643-101 Part 2/Treatment Group A by MedDRA Preferred Term in Decreasing Order of Frequency (Safety Evaluable Population)

MedDRA Preferred Term, n (%)	12 mg QD (N = 80)
Nausea	39 (48.8)
Fatigue	33 (41.3)
Thrombocytopenia/platelet count decreased[a]	27 (33.8)
Decreased appetite	22 (27.5)
Vomiting	20 (25.0)
Diarrhoea	19 (23.8)
Constipation	15 (18.8)
Anaemia	14 (17.5)
Dysgeusia	13 (16.3)
Hyperglycaemia	11 (13.8)
Blood bilirubin increased	10 (12.5)
Dehydration	9 (11.3)
Dizziness	9 (11.3)
Cough	8 (10.0)

[a] Subjects for whom both preferred terms were reported are counted only once. Overall, platelet count decreased was reported for 15 subjects, and thrombocytopenia was reported for 14 subjects.

In Part 2/TGB, there were no TEAEs reported for the single enrolled subject with AML as of the data cutoff date.

1.6.2.1.3. Part 3 Combination Therapy Dose Escalation

In Part 3/TGF, there were no TEAEs reported for the 2 enrolled subjects with AML as of the data cutoff date.

1.6.2.1.4. Drug-Drug Interaction Study of INCB057643 and Warfarin

The primary objective of this study was to determine the effect of multiple doses of INCB057643 12 mg QD on the PK and PD of warfarin after a 25 mg single oral dose administration of warfarin and the effect of warfarin on INCB057643 PK in healthy volunteers.

In Cohort 1, 17 healthy subjects received a single oral dose of 25 mg (5 × 5 mg tablets) Coumadin® (warfarin) on Day 1 and then INCB057643 12 mg QD (3 × 4 mg tablets) on Days 11 through 19, followed by a single oral dose of warfarin (5 × 5 mg tablets) on Day 13. In Cohort 2, 20 healthy subjects received INCB057643 12 mg QD (3 × 4 mg tablets) on Days 1 to 7.

With the concomitant administration of INCB057643, the geometric mean C_{max} and AUC of S- or R-warfarin increased by 9%, 1%, 9%, and 10%, respectively, and the 90% CI of geometric mean ratio (GMR) for C_{max} and AUC was within (0.8, 1.25). With the concomitant administration of warfarin, the geometric mean C_{max} and AUC of INCB057643 changed by -3.3% and +3%, respectively, and the 90% CI of GMR for C_{max} and AUC were between 0.8 and 1.25. Administration of INCB057643 alone caused approximately 35% maximal Factor VII serum concentration decrease at steady state and minimal increase of INR. Administration of warfarin alone caused approximately 50% maximal Factor VII serum concentration decrease and approximately 74% INR increase. Coadministration of INCB057643 and warfarin decreased maximal Factor VII serum concentration by approximately 70%. Comparing coadministration of INCB057643 and warfarin to warfarin alone, the geometric mean INR_{max} and $AUC_{INR,\ 0\text{-}168h}$ changed by -9.6% and -0.7%, respectively, and the 90% CI of GMR for INR_{max} and $AUC_{INR,0\text{-}168h}$ were between 0.8 and 1.25. The data from this study indicate that there is no effect on the PK of INCB057643 and warfarin, PD markers, or INR after coadministration of INCB057643 and warfarin.

In Cohort 1 Period 2, 2 subjects withdrew from study on Day 13 and Day 11, respectively. In Cohort 2, 2 subjects withdrew from study on Day 6. There were no deaths, SAEs, TEAEs of Grade 3 or higher, or TEAEs leading to treatment discontinuation in this study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

- To assess the safety and tolerability of INCB057643 as monotherapy and in combination with SOC agents in subjects with advanced malignancies.

2.1.2. Secondary Objectives

- To evaluate the PK of INCB057643 when administered as monotherapy in the fasted state and in the fed state (food effect; Part 2 only) and when administered in combination with SOC agents in the fasted state.
- To assess the PD of INCB057643 when administered as monotherapy in subjects with advanced malignancies.
- To evaluate the preliminary efficacy of INCB057643 when administered as monotherapy and in combination with SOC agents based on the investigator assessment of response using criteria appropriate for each disease in subjects with advanced malignancies.

2.2. Study Endpoints

2.2.1. Primary Endpoints

- Safety and tolerability of INCB057643 as monotherapy and in combination with SOC agents as assessed by clinical laboratory assessments, physical examinations, 12-lead ECGs, and AEs.

2.2.2. Secondary Endpoints

- C_{max}, T_{max}, C_{min}, AUC_{0-t}, and $AUC_{0-\tau}$ of INCB057643 at Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 2 Day 1 (food effect; Part 2 only).
- Pharmacodynamic profile of INCB057643 using a plasma PD assay.
- Objective response rate in subjects with measurable or evaluable disease as determined by the investigator assessment of response using the criteria appropriate for each disease.

[redacted]

3. SUBJECT ELIGIBILITY

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

3.1. Subject Inclusion Criteria

Subjects with relapsed or refractory advanced or metastatic malignancies (see Section 4.1 for detailed study population) who meet all of the following criteria may be included in the study:

1. Men and women aged 18 years or older.
2. Histologically or cytologically confirmed diagnosis of advanced malignancy:
   - **a. Part 1 – Monotherapy Dose Escalation:**
     - TGA: Advanced solid tumor or lymphoma
     - TGB: Acute leukemia (any), HR-MDS, MDS/MPN, or MF
     - TGC: MM
   - **b. Part 2 – Monotherapy Dose Expansion:**
     - TGA: Presence of measureable disease in one of the following tumor types: pancreatic adenocarcinoma, mCRPC, breast cancer, high-grade serous ovarian cancer, glioblastoma multiforme, NHL, Ewing's sarcoma, or any solid tumor or lymphoma (except specified above) with any pathway alteration relevant to BET protein signaling, such as MYC pathway activation, which is hypothesized to be susceptible to INCB057643 monotherapy (requires approval by medical monitor).
     - TGB: AML, HR-MDS, MDS/MPN, or MF
     - TGC: Measureable/evaluable MM, defined as one or more of the following:
       - Serum M-protein ≥ 0.5 g/dL
       - Urine M-protein ≥ 200 mg/24 h
       - Serum free light chain (FLC): Involved FLC level ≥ 10 mg/dL provided serum FLC ratio is abnormal
   - **c. Part 3 – Combination Dose Escalation (C-ES):**
     - C-ES-TGA: any solid tumor for which treatment with gemcitabine is relevant.
     - C-ES-TGB: any solid tumor for which treatment with paclitaxel is relevant.

- C-ES-TGC (conducted in the United States only): any solid tumor for which treatment with rucaparib is relevant.
- C-ES-TGD: any mCRPC subjects eligible to receive abiraterone plus prednisone.
  - mCRPC subjects must maintain a castrate level of testosterone documented (< 50 ng/dL) during the screening period and while on study.
- C-ES-TGE (conducted in the United States only): any MF subjects currently receiving ruxolitinib with an inadequate response, as defined below:
  - Palpable spleen of > 10 cm below the left subcostal margin on physical examination at screening OR
  - Palpable splenomegaly of 5 to 10 cm below left subcostal margin on physical examination AND active symptoms of MF at screening as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form (see Appendix P).
  - Subjects must be receiving ruxolitinib for ≥ 6 months with a stable dose for ≥ 8 weeks (acceptable doses are 5 to 25 mg BID).
- C-ES-TGF: any AML and HR-MDS subjects eligible to receive azacitidine.

d. Part 4 – Combination Dose Expansion (C-EX):

- C-EX-TGA (conducted in the United States only): any *BRCA* wild type platinum-resistant mHGSOC (epithelial ovarian/fallopian tube/primary peritoneal cancer) subjects eligible to receive rucaparib.
  - Platinum-resistant disease is defined by disease progression within 6 months of completing platinum-based therapy.
  - Known *BRCA* wild type by a validated assay before consenting.
  - Subjects must be PARP inhibitor naive or have had a clinical response (CR or partial response [PR]) to a prior PARP inhibitor and progressed and have a *BRCA* status that was shown to be *BRCA* wild type at the time of consent.
- C-EX-TGB: any mCRPC subjects who have progressed on first-line enzalutamide for metastatic disease and who are eligible to receive abiraterone plus prednisone (chemotherapy treatment naive); OR any mCRPC subjects who have demonstrated PSA progression with or without radiologic progression while being treated with abiraterone plus prednisone and who are clinically stable and will remain on abiraterone plus prednisone (prior chemotherapy is allowed).
  - Progression is defined by the Prostate Cancer Working Group 3 (PCWG3) guidelines (blood-based PSA or imaging [nodes, viscera, and bone] at study entry).
  - mCRPC subjects must maintain a castrate level of testosterone documented (< 50 ng/dL) during the screening period and while on study.

- C-EX-TGC (conducted in the United States only): any MF subjects currently receiving ruxolitinib with an inadequate response, as defined below:
  - Palpable spleen of > 10 cm below the left subcostal margin on physical examination at screening OR
  - Palpable splenomegaly of 5 to 10 cm below left subcostal margin on physical examination AND active symptoms of MF at screening as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form (see Appendix P).
  - MF subjects must be receiving ruxolitinib for ≥ 6 months with a stable dose for ≥ 8 weeks (acceptable doses are 5 to 25 mg BID).
- C-EX-TGD: any AML and HR-MDS subjects eligible to receive azacitidine.
  - Confirmed AML or HR-MDS (International Prognostic Scoring System -2 or high risk) in accordance with WHO diagnostic criteria.
  - Failure of prior therapy with HMA, defined as at least 1 of the following:
    - Progression to AML
    - % increase in bone marrow blasts
    - Relapsed disease after response
    - At least 4 cycles of treatment without clinical benefit (hematological improvement or better)

3. Prior therapy, as follows:
   a. For Parts 1 and 2/TGA and TGB, subjects must have progressed following at least 1 line of prior therapy, and there is no further established therapy that is known to provide clinical benefit (including subjects who are intolerant to, not eligible for, or refuse the established therapy).
      - Subjects with AML are eligible if they have relapsed and/or refractory disease, if they are ≥ 65 years of age and are not candidates for or have refused standard chemotherapy, or if they have no established standard of care that is known to provide clinical benefit in the judgement of the investigator.
      - Subjects with MF must be resistant, refractory, or intolerant to ruxolitinib therapy.
   b. For Parts 1 and 2/TGC, MM subjects must have relapsed from or have been refractory to ≥ 2 prior treatment regimens, including a proteasome inhibitor and an immunomodulatory drug, and have no current standard options available.
   c. For Parts 3 and 4, subjects must have progressed following at least 1 line of prior therapy, and treatment with the select SOC must be relevant for the specific disease cohort.

4. For subjects with solid tumors and lymphoma in all parts of the study (where applicable), willingness to undergo a pretreatment core or excisional tumor biopsy (except for glioblastoma) or availability of a tumor block or 25 unstained slides from biopsy or resection of primary tumor or metastasis that is preferably ≤ 1 year old and obtained after completion of last treatment. For subjects with hematologic malignancies in which bone marrow biopsy and/or aspirate is part of the disease assessment, willingness to undergo a pretreatment bone marrow biopsy and/or aspirate (as appropriate to disease). If a biopsy is not possible or contraindicated, or the tissue requirement cannot be satisfied, this may be omitted with approval from the medical monitor. In all cases, preferably, biopsies will be confirmed to contain adequate tumor tissue by a local pathology review.
5. Life expectancy > 12 weeks; for MF subjects in Parts 3 and 4, life expectancy ≥ 24 weeks.
6. ECOG performance status score:
    a. Parts 1 and 3: 0 or 1
    b. Parts 2 and 4: 0, 1, or 2
7. Willingness to avoid pregnancy or fathering children based on the criteria below:
    a. Women of childbearing potential must have a negative serum pregnancy test at screening and immediately before the first dose (within 24 hours) of study drug.
    b. Women of nonchildbearing potential are defined as surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 24 months of amenorrhea and at least 50 years of age.
    c. Men and women of childbearing potential must agree to take appropriate precautions (ie, use at least 2 forms of contraception) to avoid pregnancy or fathering children from screening through follow-up (at least 28 days after the last dose of all study medications). Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subjects and their understanding confirmed.

        Note: While double-barrier methods (a combination of male condom with either cap, diaphragm, or sponge with spermicide) are not considered highly effective per the CTFG guidance (see Appendix A), for the purposes of this study they are considered acceptable birth control methods. The treating physician is responsible for discussing acceptable methods of contraception with the subject for the purposes of this study in subjects with advanced cancer.
8. Females must agree to abstain from breastfeeding during study participation and for 28 days after study drug discontinuation.
9. Males must also agree to refrain from donating semen or sperm during treatment and for 28 days after discontinuation from this study.
10. Ability to comprehend and willingness to sign an informed consent form (ICF).

3.2. Subject Exclusion Criteria

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

1. Inadequate bone marrow function demonstrated by any of the following:

Laboratory Parameter	Part 1/ TGA	Part 2/ TGA	Parts 1 and 2/ TGC[a]	Part 3/C-ES-TGA/TGB/ TGC/TGD and Part 4/C-EX-TGA/TGB	Part 3/C-ES-TGE and Part 4/C-EX-TGC
Hemoglobin (g/dL)	< 10.0	< 8.0	< 8.0	< 9.0	Subjects unwilling to receive red blood cell transfusion to treat low hemoglobin levels are excluded.
Platelet count ($\times 10^9$/L)	< 100	< 100	< 75	< 100	< 50 in 4 weeks before screening or platelet transfusions within 8 weeks of screening.
ANC ($\times 10^9$/L)	< 1.5	< 1.0	< 1.0	< 1.5	< 0.5 in the 4 weeks before screening.

Note: No specific hematologic exclusion criteria apply for subjects with AML/HR-MDS in Parts 1 and 2/TGB, Part 3 C-ES-TGF, or Part 4 C-EX-TGD. The medical monitor will review all CBC parameters before approving enrollment into the study.

[a] Multiple myeloma subjects in Part 2 only: $< 50 \times 10^9$/L if 50% of bone marrow nucleated cells are plasma cells.

2. Inadequate organ function demonstrated by any of the following, unless due to the underlying disease and approved by the medical monitor:
   a. All Parts: Total bilirubin > 1.5 × upper limit of normal (ULN). Total bilirubin > 1.5 × ULN is acceptable if direct bilirubin ≤ 1.2 × ULN or with a diagnosis of Gilbert's syndrome.
   b. Parts 1 and 3: AST or ALT > 1.5 × ULN.
   c. Parts 2 and 4: AST and ALT > 2.5 × ULN or > 5 × ULN for subjects with liver metastases.
   d. All Parts: Creatinine clearance < 50 mL/min based on Cockroft-Gault formula or 24-hour urinalysis (< 30 mL/min for MM).
   e. All Parts: ALP ≥ 2.5 × ULN.
      - Subjects with 1) bone metastases AND 2) no hepatic parenchymal metastases on screening radiographic examinations may enroll if ALP is ≤ 5 × ULN. Subjects with 1) bone metastases AND 2) hepatic parenchymal metastases on screening radiographic examination may enroll if ALP is ≤ 5 × ULN only with medical monitor approval.
3. Receipt of anticancer medications or investigational drugs within the following intervals before the first administration of study drug, unless with medical monitor approval:
   a. < 5 half-lives or 14 days, whichever is longer, for any investigational agent.
   b. < 5 half-lives for all other chemotherapy or targeted small molecule anticancer medications.
   c. < 6 weeks for mitomycin-C or nitrosoureas.
   d. < 4 weeks for immunotherapy or antibody therapy.

e. The following concurrent medications are allowed:

- Subjects with mCRPC may be maintained on androgen deprivation, chemical or surgical, at the discretion of the investigator, with a castrate level of testosterone documented (< 50 ng/dL) during the screening period and while on study.
- Low-dose corticosteroids (prednisone or the equivalent ≤ 10 mg per day) may be administered. Use of inhaled or topical steroids and prophylactic corticosteroids for radiographic procedures is permitted.
- For hematologic malignancies: Hydroxyurea for controlling proliferative disease may be administered. Hydroxyurea should not be used within at least 48 hours before and on the day of the [redacted] sample collection (bone marrow and blood) or during or 72 hours before or after azacitidine administration.
- For Parts 1 and 2/TGC: Receipt of less than 160 mg dexamethasone within 14 days before receiving the first dose of study drug is allowed.
- Denosumab and zoledronic acid are permitted to treat cancer-related bone diseases.

4. Prior receipt of any BET inhibitor.
5. Unless approved by the medical monitor, may not have received an allogeneic hematopoietic stem cell transplant within 6 months before treatment, or have active graft-versus-host-disease following allogeneic transplant, or have received immunosuppressive therapy following allogeneic transplant within 2 weeks of Cycle 1 Day 1.
6. Unless approved by the medical monitor, may not have received autologous hematopoietic stem cell transplant within 3 months before treatment.
7. Any unresolved toxicity ≥ Grade 2 (except stable Grade 2 peripheral neuropathy or alopecia) from previous anticancer therapy.
8. Radiotherapy within the 2 weeks before initiation of treatment. Palliative radiation treatment to nonindex or bone lesions performed less than 2 weeks before treatment initiation may be considered with medical monitor approval. For Part 3/C-ES-TGE and Part 4/C-EX-TGC, MF subjects may not have splenic irradiation within 6 months of the first dose of INCB057643.
9. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
10. Type 1 diabetes or uncontrolled Type 2 diabetes.
    a. All Parts: HbA1c of ≥ 8% (all subjects will have HbA1c test at screening).
    b. For Parts 1 and 3 only: Fasting blood glucose > 160 mg/dL (> 8.9 mmol/L)
11. Known human immunodeficiency virus infection (HIV; HIV 1/2 antibodies).
12. Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as defined in Section 7.5.5.3.

13. Currently active and uncontrolled infectious disease requiring systemic antibiotic, antifungal, or antiviral treatment.
14. Untreated brain or CNS metastases or brain/CNS metastases that have progressed (eg, evidence of new or enlarging brain metastasis or new neurological symptoms attributable to brain/CNS metastases). Subjects with previously treated and clinically stable brain/CNS metastases and off all corticosteroids for ≥ 2 weeks before Cycle 1 Day 1 are eligible. Primary CNS lymphoma will only be permitted in Part 2/TGA. Subjects with glioblastoma are not subjected to this criterion with medical monitor approval.
15. History or presence of abnormal ECG that, in the investigator's opinion, is clinically meaningful. A screening QTc interval of > 470 msec is excluded. For subjects with an intraventricular conduction delay (QRS interval ≥ 120 msec) the JTc interval may be used in place of the QTc with sponsor approval. Subjects with left bundle branch block are excluded. Subjects with QTc prolongation due to a pacemaker may enroll if the JT is normal or with medical monitor approval. In the event that a single QTc is > 470 msec, the subject may enroll if the average QTc for the 3 ECGs is < 470 msec. QTcF is preferred QT correction formula.
16. History (≤ 1 year) of clinically significant or uncontrolled cardiac disease, acute myocardial infarction, New York Heart Association Class III or IV congestive heart failure, or clinical significant arrhythmia not controlled by standard-of-care therapy. Subjects with a pacemaker and well-controlled rhythm for at least 1 month before first dose of study drug will be allowed.
17. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
18. Unless approved by the medical monitor, current use of prohibited medication as described in Section 5.6.2.
19. Unless approved by the medical monitor, use of any potent CYP3A4 inhibitors or inducers (Appendix N) within 14 days or 5 half-lives (whichever is longer) before the first dose of study drug.
20. Known hypersensitivity or severe reaction to INCB057643, similar compounds, or excipients of INCB057643 (refer to the IB).
21. Subjects who, in the opinion of the investigator, are unable or unlikely to comply with the dose schedule and study evaluations.
22. Unable to swallow and retain oral medication.
23. Currently breastfeeding.
24. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug or any of the SOC agents and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
25. Inability to comprehend or unwilling to sign the ICF.

26. Any sign of clinically significant bleeding within 14 days of Cycle 1 Day 1.
27. International normalized ratio, prothrombin time (PT), and activated partial thromboplastin time (aPTT) > 1.5 × ULN (unless the subject is receiving anticoagulant therapy, in which case, the subject may be included as long as the INR, PT, and aPTT are within therapeutic range of intended use of anticoagulants).
    Note: Partial thromboplastin time may be used in place of aPTT per institutional standards.
28. All parts of the study (where applicable) for solid tumors and lymphomas: Subjects with a history of bleeding related to cancer under study requiring a medical intervention (eg, embolization procedure, red blood cell transfusion, or hospitalization) within 30 days of study enrollment.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label, dose-escalation/dose-expansion study of INCB057643 as monotherapy or in combination with SOC agents in subjects with relapsing or refractory advanced malignancies. Subjects will receive INCB057643 continuously administered orally in 21- or 28-day cycles, as applicable to regimen schedules in combination (see Section 5.2 for details). Alternative administration schedules may be assessed if indicated by emerging safety, PK, or PD data. The study consists of 4 parts. Parts 1 and 2 will evaluate INCB057643 as monotherapy, and Parts 3 and 4 will evaluate INCB057643 in combination with SOC agents.

The study began with Part 1, Monotherapy Dose Escalation, which will determine the MTD of INCB057643 and/or a tolerated dose that reaches the desired target inhibition (ie, a pharmacologically active dose [PAD]; plasma concentration exceeding *ex vivo* or projected c-Myc IC_{50} for approximately 6-12 hours or achieves clinical response). Part 1 will be conducted in 3 disease-specific treatment groups.

Part 2, Monotherapy Dose Expansion, will further evaluate the safety, preliminary efficacy, PK, and PD of the treatment group–specific dose selected in Part 1 (at ≤ the MTD) in select tumor types postulated to be particularly susceptible to inhibition of BET proteins. See Figure 2 for the study design of Parts 1 and 2.

Part 3, Combination Dose-Escalation (C-ES), will determine the MTD and/or a tolerated dose (the RP2D) of the combination of INCB057643 with one of the SOC agents. Part 3 will be conducted in 6 disease-specific treatment groups.

Part 4, Combination Dose-Expansion (C-EX), after identification of the RP2D in combination regimens in Part 3, will further determine safety, tolerability, efficacy, PK, and PD. Part 4 will be conducted in 4 treatment groups. The sponsor may decide not to expand any or some cohorts.

As a follow-up to the data cutoff date of 19 JAN 2018, screening and enrollment was placed on hold by the sponsor in MAR 2018, due to a less favorable benefit/risk assessment based on emerging data, which was mainly histopathological finding of cardiac myopathy observed in the preclinical 3-month toxicology study in monkeys (Section 1.5.1). Furthermore, all subjects were asked to reconsent if they were opting to continue receiving study treatment at the discretion of

the investigators and receive INCB057643 ≤ 8 mg QD. Therefore, as of MAR 2018, no further subjects are being enrolled in Parts 1, 2, and 3, and Part 4 will not be opened for enrollment.

4.1.1. Part 1 – Monotherapy Dose Escalation

The study began with dose escalation in Part 1. Part 1 comprises 3 disease-specific treatment groups. Each treatment group will use a 3 + 3 design to determine the tolerated dose over a 21-day cycle. See Figure 2 for the study design of Parts 1 and 2.

- Treatment Group A (TGA) will include subjects with any advanced solid tumor or lymphoma.
- Treatment Group B (TGB) will include subjects with acute leukemia, HR-MDS, MDS/MPN, or MF.
- Treatment Group C (TGC) will include subjects with MM.

Enrollment into the study began in TGA. The initial dose level was 8 mg QD. Once a PAD has been identified in TGA, TGB and TGC will begin parallel enrollment at that PAD. Subsequently, dose escalation will proceed independently in the 3 treatment groups to an MTD (or a tolerated PAD if an MTD is not reached), each using a 3 + 3 design. If there is a distinct discrepancy in tolerability among different disease types within the same treatment group, additional disease-specific dose-escalation schedules may be initiated.

Each dose-escalation cohort will initially enroll at least 3 subjects. If no DLTs are observed in the initial 3 subjects, another cohort will begin enrollment at the next highest dose level. Dose escalations between cohorts may be up to 100% until a DLT is observed, after which dose escalations in the relevant treatment group will be limited to no more than 50% above the previous level. Dose escalations will be accomplished using the following options: 1) increasing the number of tablets taken at each QD administration, or 2) increasing administration frequency to BID, or 3) increasing the number of tablets taken at 1 or more dose administrations and increasing the frequency to BID. Subjects will continue to receive INCB057643 in 21-day cycles until withdrawal criteria are met (eg, toxicity, disease progression).

If 1 DLT is observed in the first 3 subjects, at least 3 additional subjects will be enrolled in that cohort. If a DLT occurs in one-third or more of the total cohort (ie, ≥ 2 of 6 subjects), then the MTD will be deemed to have been exceeded, and the next lower dose level will be deemed to be the tolerated dose. Thus, the MTD will be defined as 1 dose level below the nontolerated dose (NTD) at which one-third or more of subjects in a particular cohort report DLTs. If the first cohort exceeds the MTD, a dose de-escalation will be considered.

The sponsor, in consultation with participating investigators, may elect to investigate 1 or more dose levels less than the NTD or expand a dose cohort(s) deemed tolerable up to 12 subjects in order to obtain additional PK, PD, and safety data before determining the MTD. At the end of Cycle 1, subjects who took ≥ 80% of planned doses of INCB057643 (eg, 17 of 21 doses) during the study observation period or experience a DLT will be included in the evaluation cohort. See Section 5.4.1.1 for DLT criteria.

Individual subjects within each cohort will undergo reductions/interruptions in INCB057643 administration according to prescribed safety parameters. Subjects tolerating INCB057643 at the

assigned dose for at least 4 cycles may be considered for a dose increase if a higher dose has been found to be tolerated in a subsequent cohort (see Section 5.4.5 for details).

4.1.2. Part 2 – Monotherapy Dose Expansion

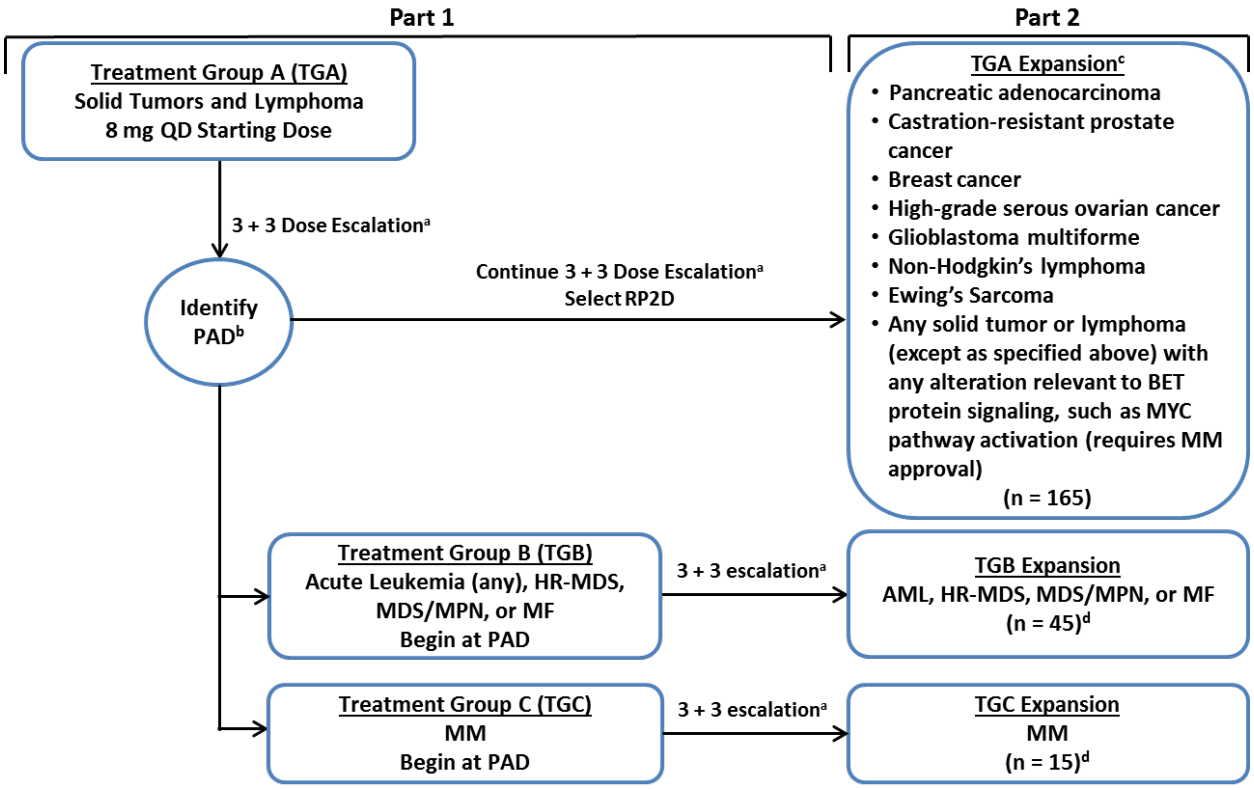
Part 2 of the study will evaluate the treatment group–specific dose selected in Part 1 in specific tumor types postulated to be particularly susceptible to inhibition of BET proteins. See Figure 2 for the study design of Parts 1 and 2. A dose up to the MTD may be selected for use in each expansion cohort by the sponsor and investigators. More than 1 dose of INCB057643 and/or schedule may be assessed, pending emerging safety, PK, and PD data. Part 2/TGA will enroll up to approximately 165 subjects with specified solid tumors or lymphoma (see Section 3.1). The high-grade serous ovarian cancer cohort will include approximately 20 subjects. At least 5 of these subjects will have BRD4 amplification, and at least another 5 will have MYC amplification/ overexpression/translocation. The BRD4 and MYC molecular signature will be identified for enrollment eligibility by known status before subjects sign the ICF. The mCRPC cohort will include approximately 20 subjects. At least 5 of these will have AR-V7 identified for enrollment eligibility by known status before subjects sign the ICF, and another 5 will have poorly differentiated neuroendocrine phenotype identified by local investigators and pathologists before subjects sign the ICF. An NHL cohort will include approximately 45 subjects, 5 to 15 of those having a diagnosis of "double-hit" or "triple-hit" (overexpression and/or translocation of MYC and BCL2 and/or BCL6) diffuse large B-cell lymphoma (DLBCL), 5 to 15 of those having a diagnosis of follicular lymphoma, and 5 to 15 of those to enroll other NHLs such as DLBCL, Burkitt's lymphoma, or B-cell lymphoma, unclassifiable (BCLU; with features intermediate between DLBCL and Burkitt's lymphoma). The other disease-specific and molecularly defined groups in TGA, (pancreatic adenocarcinoma, breast cancer, glioblastoma multiforme, and Ewing's sarcoma; see Section 3.1) will enroll approximately 5 to 15 subjects each. Efforts should be made to identify subjects with a pathway alteration relevant to BET signaling such as MYC or BRD amplification in these tumor types. An additional group of up to approximately 20 subjects with any other tumor (except those specified previously) known to have pathway alteration relevant to BET protein signaling will also be enrolled. Part 2/TGB will enroll approximately 45 subjects (5 to 15 in each tumor type) with AML, HR-MDS, MDS/MPN, and MF. Part 2/TGC will enroll initially 5 to 15 subjects with MM.

If ≥ 33% of subjects in a Part 2 expansion cohort experience DLTs during Cycle 1, then further enrollment to the cohort will be stopped, and a lower dose level may be explored.

During dose escalation and expansion, the small number of subjects in each group and heterogeneity of dose and subject characteristics within the groups is the reason for not having predefined efficacy stopping criteria.

Individual dose titration will be permitted according to Protocol-defined safety parameters. Subjects will continue to receive INCB057643 in 21-day cycles until withdrawal criteria are met (eg, toxicity, disease progression). Additional PK assessments for food effect on drug exposure will be performed in the first 12 subjects enrolled into Part 2/TGA. Additional subjects may be enrolled if there are data quality issues among the initial 12 subjects.

Figure 2: Part 1 and Part 2 Monotherapy Dose Escalation and Expansion Study Design



[a] Increments up to 100% until DLT occurs within a given treatment group, then up to 50% thereafter.
[b] Defined as plasma concentration exceeding *ex vivo* or projected c-Myc IC_{50} for 8 to 12 hours or achieves clinical response.
[c] Part 2/TGA Expansion: The high-grade serous ovarian cancer group will include approximately 20 subjects; at least 5 of which will have BRD4 amplification and another 5 will have MYC amplification/overexpression/ translocation. The BRD4 and MYC molecular signature will be identified by known status before subject screening. The mCRPC cohort will include approximately 20 subjects; at least 5 of which will have AR-V7 and at least another 5 of which will have poorly differentiated neuroendocrine phenotype. The AR molecular signature will be identified by known status before subject screening. The NHL cohort will include approximately 45 subjects; 5 to 15 of which will have a diagnosis of "double-hit" or "triple-hit" DLBCL, 5 to 15 of which will have follicular lymphoma, and 5 to 15 of which to enroll other NHLs such as Burkitt's lymphoma or BCLU (with features intermediate between DLBCL and Burkitt's lymphoma). The other tumor type cohorts in the Part 2/TGA expansion will enroll approximately 5 to 15 subjects each. An additional group of up to approximately 20 subjects with any tumor (except separately listed) known to have pathway alteration relevant to BET protein signaling will also be enrolled. Part 2/TGA expansion may enroll up to approximately 165 subjects.
[d] Part 2/TGB Expansion will enroll 5 to 15 (each tumor type) subjects with AML, HR-MDS, MDS/MPN or MF for a possible total of up to 45 subjects; Part 2/TGC Expansion will enroll 5 to 15 subjects with MM for a possible total of up to 15 subjects.

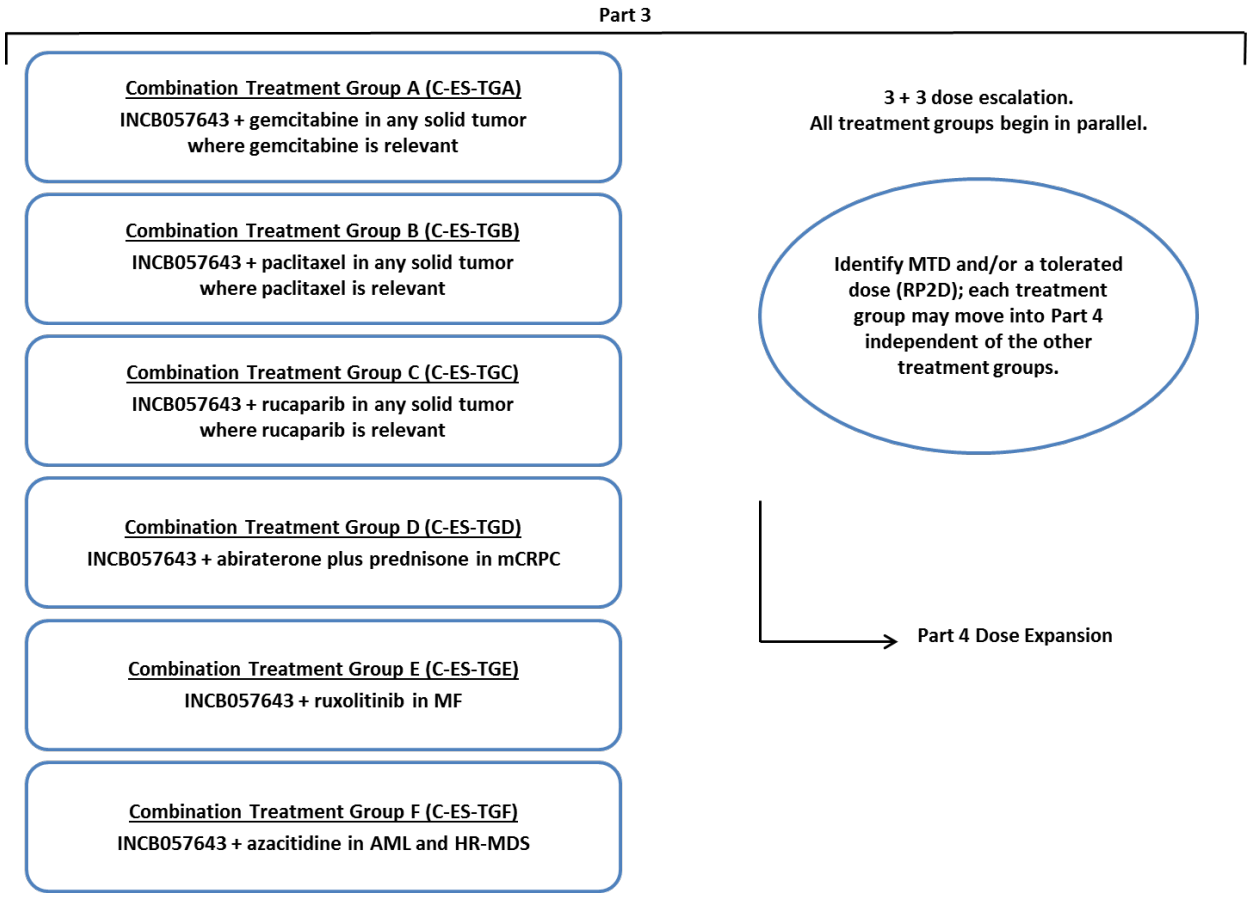
4.1.3. Part 3 – Combination Dose Escalation (C-ES)

Part 3 will determine the MTD and/or a tolerated dose (the RP2D) of the combination of INCB057643 and one of the SOC agents in relapsed or refractory advanced or metastatic solid tumor and hematologic malignancies. See Figure 3. The starting dose of INCB057643 in the combination treatment groups will be the PAD or 1 dose level below the MTD of INCB057643 monotherapy identified in Part 1 of this study. Pending emerging data in Part 1 and Part 2, a lower starting dose of INCB057643 could be selected for all or several combinations in Part 3 (eg, 2 dose levels below the MTD of INCB057643 in Part 1). Starting doses of the SOC combination agents will be selected from conventional dose regimens for the first dose cohort and can be modified for the subsequent cohorts, pending emerging safety data. INCB057643 doses will not exceed the monotherapy MTD identified in Part 1.

Combination treatment groups will escalate independently and in parallel until the MTD and/or a tolerated dose (the RP2D) of the combinations is identified and will be followed by independent expansion cohorts at the selected dose(s) in Part 4. Pending emerging data, more than 1 RP2D dose could be explored in each expansion cohort in Part 4.

Dose escalation will follow the 3 + 3 design. The sponsor, in consultation with participating investigators, may elect to expand a dose cohort(s) deemed tolerable to up to 12 subjects in order to obtain supplemental PK, PD, and safety data. See Section 3 for subject eligibility.

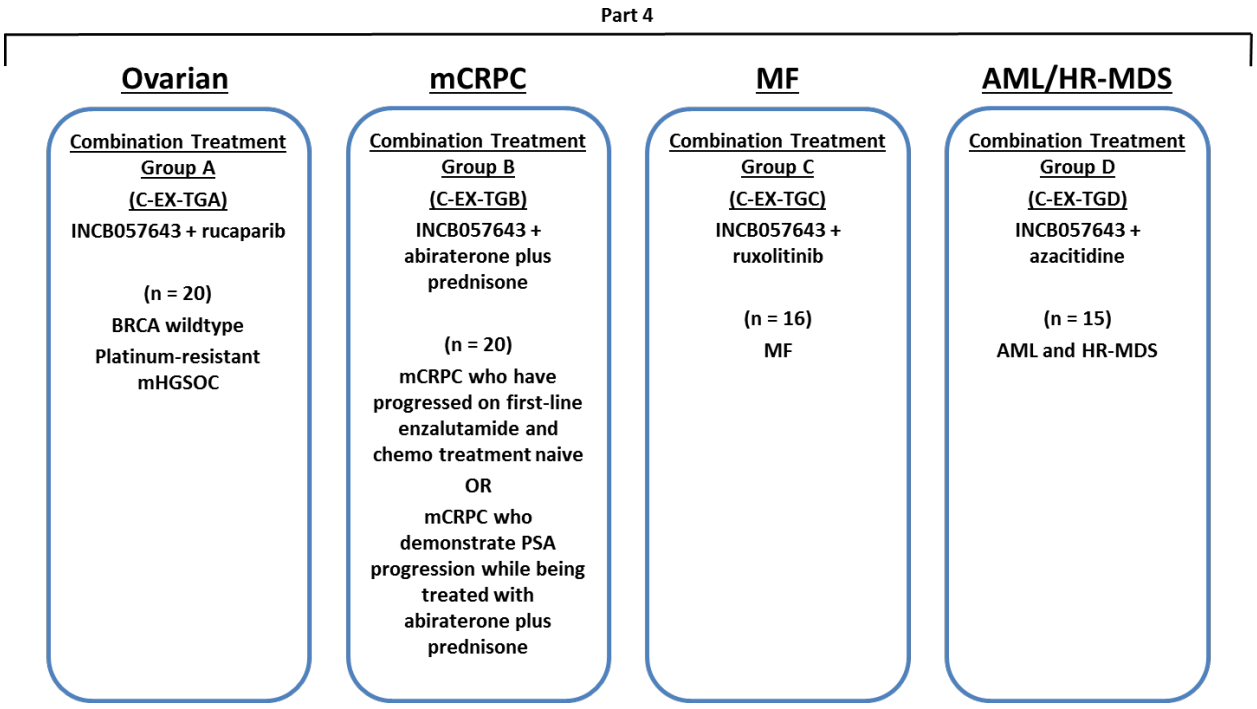
Figure 3: Part 3 Combination Dose Escalation Study Design



4.1.4. Part 4 – Combination Dose Expansion (C-EX)

After identification of the RP2D in combination regimens in Part 3, Part 4 will enroll subjects with select relapsed or refractory advanced or metastatic solid tumor and hematologic malignancies to further determine safety, tolerability, efficacy, PK, and PD in the treatment groups presented in Figure 4. The sponsor may decide not to expand any or some cohorts pending emerging data. See Section 3 for subject eligibility.

Figure 4: Part 4 Combination Dose Expansion Study Design



4.2. Number of Subjects

4.2.1. Planned Number of Subjects

- **Part 1:** 3 to 10 subjects may be enrolled per cohort per treatment group (3 treatment groups/approximately 60 subjects). See Figure 2.
- **Part 2:** 225 subjects may be enrolled across 3 treatment groups. See Figure 2.
- **Part 3:** 3 to 10 subjects may be enrolled per cohort per treatment group (6 treatment groups/approximately 60 subjects). See Figure 3.
- **Part 4:** Approximately 71 subjects may be enrolled across 4 treatment groups. See Figure 4.
- Approximately 19 centers are planned to participate in this study in the United States and in the European Union.

4.2.2. Replacement of Subjects

During Part 1 and Part 3, subjects will be replaced for any of the following reasons:

- Subjects who have not received at least 80% of planned INCB057643 doses during the 21- or 28-day DLT observation period. For INCB057643 QD dosing, a 21-day cycle would require at least 17 doses; a 28-day cycle would require at least 23 doses.
- Subjects who do not meet the eligibility requirements of the study (see Section 3).

4.3. Measures Taken to Avoid Bias

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

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Each subject enrolled in the study may continue to receive study treatment in continuous 21- or 28-day cycles. When the subject discontinues INCB057643, the treatment period will end and the subject will enter the follow-up period (see Section 6.2). Treatment duration will vary significantly between subjects but is expected to average approximately 4 to 6 months.

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. The end of the study will occur when all subjects have discontinued study drug and have completed applicable follow-up assessments. The overall duration of the study is expected to be approximately 24 months.

4.6. Study Termination

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

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

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Study sites will enter subject demographic and baseline data into the interactive voice/web response technology (IRT) in order to receive a subject number.

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

Site staff will contact the IRT to enter the quantities of study drug that are received from the sponsor and what has been dispensed to the subjects. Refer to the IRT manual for detailed information.

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

5.1.2. Randomization and Blinding

Not applicable.

5.2. Study Drugs

5.2.1. INCB057643

5.2.1.1. Description and Administration

Physical and chemical properties of INCB057643 are summarized in the IB. INCB057643 is formulated as 4 mg immediate-release tablets. The tablet is round and white to off-white and contains the active drug substance along with compendial grade excipients lactose monohydrate, sodium starch glycolate, and magnesium stearate.

Subjects will self-administer INCB057643 orally QD, as instructed by the investigator. It will be administered in the clinic on the schedule outlined in Section 6. INCB057643 doses should be taken in the morning on an empty stomach when possible. Subjects will fast for approximately 2 hours before and 1 hour after INCB057643 administration, except on days when serial PK and PD sampling is conducted, then subjects will fast at least 8 hours before the study drugs or as indicated in Section 7.8. If a dose is missed by more than 8 hours, then the subject should skip that dose and take next scheduled dose at the usual time. The sponsor may implement alternate administration, such as intermediate doses, alternate dosing schedules, or alternate formulations, depending on PK, PD, and safety results. Subjects will continue to receive combination therapy as long as they are deriving benefit and have not met any of the Protocol-defined conditions for discontinuation of treatment. Intra-subject dose escalation is not permitted in combination therapy treatment groups.

The starting dose in Part 1/TGA was 8 mg QD. The starting dose of INCB057643 in Part 2 will be the PAD or 1 dose level below the MTD of INCB057643 monotherapy identified in Part 1 of the study. The starting dose of INCB057643 in Part 3 C-ES-TGA/TGB/TGC/TGD will be 8 mg QD, identified as the PAD, and 1 dose level below the MTD of 12 mg QD identified in Part 1/TGA of the study (Section 1.6) in a 21- or 28-day continuous treatment cycle, depending on the SOC agent being administered in combination. Pending emerging data in Part 1 and Part 2, a lower starting dose of INCB057643 could be selected for all or several combinations in Part 3 (eg, 2 dose levels below the MTD of INCB057643 in Part 1). The starting dose of INCB057643 in Part 4 will be the treatment group–specific RP2D identified in Part 3.

5.2.1.2. Supply, Packaging, and Labeling

INCB057643 will be provided as 4 mg tablets packaged in high-density polyethylene bottles. No preparation is required. All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country and will state "Caution: New Drug—Limited by Federal (or United States) law to investigational use."

5.2.1.3. Storage

INCB057643 drug product should be stored at ambient conditions (15°C-30°C or 59°F-86°F).

5.2.1.4. Dispensing Study Drug

An initial bulk supply of INCB057643 will be provided to investigative sites by Incyte before enrollment of the first subject. When dispensing to subjects, the investigator or designee will contact the IRT system, remove the appropriate quantity of study drug from their stock, dispense the medication, and enter the amount dispensed into the eCRF and drug accountability log. Full details will be provided in the Study Manual.

5.2.1.5. Instruction to Subjects for Handling Study Drug

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

- To store the study drug at room temperature.
- To only remove from the study drug bottle the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To fast for approximately 2 hours before and 1 hour after INCB057643 administration.
- If a dose is missed by more than 8 hours, then the subject should skip that dose and take next scheduled dose at the usual time.
- To report any missed doses.

- If the subject vomits after taking study drug, the subject should not take another dose; dosing should be resumed at the next scheduled dose.
- To keep study drug in a safe place and out of reach of children.

To bring all used and unused study drug kits to the site at each visit.

5.2.2. Standard of Care Agents

Conventional regimens of the SOC agents will be used throughout Part 3 and Part 4 of the study (see Table 6). Subjects will continue to receive combination therapy as long as they are deriving benefit and have not met any of the Protocol-defined conditions for discontinuation of treatment. Dosing adjustment (dosing delay and/or dose reduction) during treatment is allowed. Intra-subject dose-escalation is not permitted.

5.2.2.1. Gemcitabine Administration

Gemcitabine will be administered as 1000 mg/m^2 by a 30-minute IV infusion (± 5 min), on Days 1 and 8 of each 21-day cycle. Subjects may receive prophylactic granulocyte colony-stimulating factor (G-CSF) support with filgrastim (Neupogen®) per institutional guidelines, however, it should not be given in the first cycle unless discussed with the medical monitor.

5.2.2.2. Paclitaxel Administration

Paclitaxel will be administered as 80 mg/m^2 by a 1-hour IV infusion (± 15 min) on Days 1, 8, and 15 of each 21-day cycle. Treatment continuation following clinical response will be at the discretion of the investigator. Subjects must receive premedications (IV or PO) with corticosteroids, H1- and H2-antagonists, antihistamines, and antiemetics based on institutional guidelines, investigator practice, or local prescribing information or standards of care. Subjects may receive prophylactic G-CSF support with filgrastim (Neupogen) per institutional guidelines, however, it should not be given in the first cycle unless discussed with the medical monitor.

5.2.2.3. Rucaparib Administration

Rucaparib will be administered as 600 mg (two 300 mg tablets) PO BID in a continuous dosing regimen with or without food. This oral agent is prepared as 200, 250, and 300 mg tablets.

5.2.2.4. Abiraterone Administration

Abiraterone will be administered as 1000 mg (two 500 mg tablets or four 250 mg tablets) PO QD in a continuous dosing regimen in combination with prednisone 5 mg PO BID. Abiraterone should be taken on an empty stomach; no food should be consumed for at least 2 hours before the dose is taken and for at least 1 hour after the dose is taken.

5.2.2.5. Ruxolitinib Administration

Ruxolitinib will be administered as a dose of 5 to 25 mg PO BID in a continuous dosing regimen using the dose designated as the stable dose at the time of screening for each subject. Doses of ruxolitinib should be self-administered approximately 12 hours apart without regard to food.

5.2.2.6. Azacitidine Administration

Azacitidine will be administered as a dose of 75 mg/m^2 IV or SC for 7 days during a 9-day or less period (ie, a 2-day break allowed on weekend, if needed) of each 28-day treatment cycle.

5.2.2.7. Supply, Packaging, and Labeling

In countries where reference therapies (or their generic equivalents) are commercially available, investigators are responsible for ensuring that subjects receive commercially available supplies of these therapies for the entire duration of study participation. Incyte may provide certain reference therapies where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to these therapies. The contents of the labels will be in accordance with all applicable regulatory requirements.

Table 6: Standard of Care Agent Administration

SOC Agent	Dose	Route and Administration	Cycle
Gemcitabine	1000 mg/m^2	IV, Days 1 and Day 8 of each cycle	21-day cycle
Paclitaxel	80 mg/m^2	IV, Days 1, 8, and 15 of each cycle	21-day cycle
Rucaparib	600 mg	PO, two 300 mg tablets BID; continuous with or without food	21-day cycle
Abiraterone	1000 mg	PO, two 500 mg tablets QD; continuous plus prednisone 5 mg BID on empty stomach	21-day cycle
Ruxolitinib	Stable dose at screening such as 10-50 mg	PO, 5-25 mg BID; continuous without regard to food	21-day cycle
Azacitidine	75 mg/m^2	IV or SC, 7 days during a 9-day or less period of each cycle	28-day cycle

5.3. Treatment Compliance

Compliance with all study-related medications should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study.

INCB057643, rucaparib, abiraterone + prednisone, and ruxolitinib are oral medications, and compliance will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor or the sponsor's designee (tablet counts). Subjects will be instructed to bring all study drugs with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance. Drug accountability will not be captured in InForm for standard-of-care agents used in this study.

Gemcitabine, paclitaxel, and azacitidine are administered as either IV or SC infusions by the site personnel. Receipt of infusions will be documented by the site staff and monitored by the sponsor or the sponsor's designee.

5.4. Dose Modifications

5.4.1. Study Drug – Part 1 and Part 3

Selections and modifications to the study drug regimen are planned for dose-escalation cohorts (Part 1 and Part 3). Dose interruptions and modifications also may occur for individual study subjects. The identification of DLTs will define the doses used in planned cohorts. Further, for both INCB057643 and any of the other chemotherapy regimens, the occurrence of DLTs and other toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual subjects.

Subjects enrolled in the dose-escalation portion of the study will have the option of escalating to a dose found to be tolerated in a subsequent cohort, as per Section 5.4.5.

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

Specific toxicities occurring during Cycle 1 of Part 1 and Part 3 will be considered to be DLTs if they meet the definition of a DLT, as defined below (see Table 7). All DLTs will be assessed by the investigator using CTCAE v4.03.

In Part 1 and Part 3, subjects who took at least 17 of 21 (≥ 80%) prescribed doses (21-day cycle) or 23 of 28 (≥80%) prescribed doses (28-day cycle) of INCB057643 during Cycle 1 or had a DLT will be included in the evaluation cohort. Additional subjects will be enrolled to achieve a minimum of 3 evaluable subjects in the cohort if there are discontinuations or dose interruptions that result in a subject being nonevaluable for dose evaluation.

Individual subject dose reductions may be made based on events observed at any time during treatment with study drug; however, for the purposes of determining the tolerated dose of INCB057643 in Part 1 and Part 3, decisions will be made based on events that are observed from the first day of study drug administration through and including the final day of Cycle 1.

Table 7: Definition of Dose-Limiting Toxicity

Nonhematologic toxicity		
• Any ≥ Grade 3 nonhematologic toxicity EXCEPT: – Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours – Any nonhematologic toxicity clearly and incontrovertibly related to the underlying disease or its progression – Alopecia – Grade 3 fatigue, asthenia, fever, anorexia, or constipation – Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered DLTs if fasting blood glucose is elevated [≥ Grade 3] on 2 separate occasions 3 days apart).		
Hematologic toxicity		
Parameter	**Treatment Group/Cohort**	**Toxicity**
Anemia	All	Any Grade 4, unexplained by underlying disease.
Neutropenia	Part 1/TGA; Part 3/ C-ES-TGA/TGB/TGC/TGD	Any Grade 4.
	Part 1/TGB; Part 3/ C-ES-TGE/TGF	Grade 4 with a hypocellular bone marrow lasting ≥ 6 weeks after the start of a course in the absence of residual disease.
	Part 1/TGC	Any Grade 4 lasting > 7 days.
Febrile neutropenia	Part 1/TGA and TGC; Part 3/C-ES-TGA/TGB/ TGC/TGD	Febrile neutropenia of any duration (ANC < 1.0×10^9/L and fever ≥ 38.5°C)
Thrombocytopenia	Part 1/TGA and TGC; Part 3/C-ES-TGA/TGB/ TGC/TGD	Grade 3 or higher with clinically significant bleeding or any requirement for platelet transfusion outside of institutional practice.
Other toxicities not meeting DLT criteria		
• While the rules for adjudicating DLTs in the context of dose escalation are specified above, an AE not listed above may be defined as a DLT after a consultation with the sponsor and investigators, based on the emerging safety profile.		

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

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

5.4.1.3. Follow-Up of Dose-Limiting Toxicities

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

5.4.1.4. Procedures for Cohort Review and Dose Escalation

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

5.4.2. INCB057643 Dose Interruptions and Reductions

Treatment with INCB057643 may be delayed up to 2 weeks (14 days) to allow for resolution of toxicity. Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any subject whose treatment has been delayed for more than 14 days before restarting treatment with INCB057643.

Because subjects may enter the study with extensive pretreatment and/or severe bone marrow infiltration by the primary disease, these dose reduction rules are provided as guidelines (see Table 8). In general, these guidelines should be followed for all the AEs *unless the event can clearly be determined to be UNRELATED to the study drug*. ALT/AST elevations should be managed as described in Table 8. Thrombocytopenia, neutropenia, and anemia should be managed according to the guidelines (Table 8). *In general, study drug should be interrupted for Grade 3 AEs and not resumed until the event improves to ≤ Grade 1, at which point it may be resumed at the next lower dose level. In general, study drug should be permanently discontinued for Grade 4 AEs. Exceptions can be made for the hematologic toxicities (thrombocytopenia, neutropenia, and anemia) without clinical consequence (eg, no fever, infection, bleeding)*. Other transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may also be exempt from dose-reduction rules. Hematologic events (eg, thrombocytopenia, anemia, neutropenia) occurring in Part 1 precipitating dose interruptions during Cycle 1 of treatment will be evaluated as potential DLTs (Table 7) Hematologic AEs that precipitate dose interruptions should be monitored for recovery at least every 3 days, if feasible. Other AEs should follow the guidelines for their management according to the section of "GENERAL TOXICITIES" in Table 8.

Table 8: Guidelines for Interruption and Restarting of INCB057643

GENERAL TOXICITIES	
Adverse Event	**Action Taken**
• Any Grade 1 or Grade 2 toxicity	Continue INCB057643 and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care	1. Interrupt INCB057643 up to 2 weeks (14 days), until toxicity resolves to ≤ Grade 1. 2. Restart INCB057643 at next lower dose (or 25% reduction, whichever is the smaller increment, rounded down to the nearest pill strength); monitor as clinically indicated.
• Any recurrent Grade 3 toxicity after 2 dose reductions	Discontinue INCB057643 and follow-up per Protocol. (Exceptions require approval of sponsor.)
• Any other Grade 4 toxicity	Discontinue INCB057643 and follow-up per Protocol.

Table 8: Guidelines for Interruption and Restarting of INCB057643 (Continued)

CHEMISTRY	
Adverse Event	**Action Taken**
• Grade 3 AST and/or ALT is > 5.0 and < 20.0 × ULN In subjects with liver metastasis-related elevations at baseline, contact sponsor to discuss clinical management.	• Interrupt INCB057643 up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1. • Monitor LFTs at least weekly until the toxicity has resolved to ≤ Grade 1. • If resolved within 14 days after INCB057643 interruption, restart INCB057643 at next lower dose (or at 25% reduction, rounded down to the nearest pill strength); monitor as clinically indicated. • If not resolved to ≤ Grade 1 or baseline within 14 days after INCB057643 interruption, discuss with medical monitor. • Complete a coagulation panel on the subject. • Evaluate for potential Hy's law case (Appendix Q). • Carefully examine subject's concomitant medications for any that may contribute to LFT elevations. Hold these concomitant medications or switch to an alternative; consult medical monitor, if needed.
• Grade 4 AST and/or ALT is ≥ 20.0 × ULN In subjects with liver metastasis-related elevations at baseline, contact sponsor to discuss clinical management.	Discontinue INCB057643.
• Total bilirubin > 2 × ULN In subjects with Gilbert's syndrome, contact sponsor to discuss clinical management.	Evaluate for potential Hy's Law case (Appendix Q): • If < 3 × ULN, monitor at least weekly until resolved to ≤ Grade 1. • If > 3 × ULN, interrupt treatment, when resolved to ≤ Grade 1, restart INCB057643 at the next lower dose. • If >10 × ULN, discontinue INCB057643.
• ALT > 3.0 × ULN, ALP < 2 × ULN, and bilirubin ≥ 2.0 × ULN (Hy's Law), and no other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.	Discontinue INCB057643.

Table 8: Guidelines for Interruption and Restarting of INCB057643 (Continued)

HEMATOLOGY			
Parameter	**Treatment Group/ Expansion Cohort**	**Adverse Event**	**Action Taken**
* Platelet count ($\times 10^9$/L)	Part 1/TGA; Part 1/TGC; Part 3/C-ES-TGA/ TGB/TGC/TGD	25 to < 50	• Hold until resolved to ≥ 75 if baseline was > 100; or hold until resolved to ≥ 50, if baseline was > 75; monitor CBC approximately every 3 days. • Restart INCB057643 at same dose and monitor. • At second occurrence, restart INCB057643 at next lower dose and monitor.
		< 25	• Discontinue INCB057643 if symptomatic. • If asymptomatic: – Hold until resolved to ≥ 75, if baseline was > 100; or hold until resolved to > 50, if baseline was > 75; monitor CBC approximately every 3 days. – Restart INCB057643 at a reduced dose; consult medical monitor if needed. – At second occurrence, discontinue INCB057643.
	Parts 1 and 2/TGB; Part 3/C-ES-TGF; Part 4/C-EX-TGD	N/A	Thrombocytopenia should be managed as per institutional standard, relevant to the underlying disease. Consult with the medical monitor for management outside of the institutional standard.
	Part 3/C-ES-TGE; Part 4/C-EX-TGC	≥ 50% decrease from baseline platelet count	• Evaluate underlying disease • Consider dose interruption if cytopenias are NOT due to underlying disease or treatment with SOC agents. • Restart INCB057643 at next lower dose (or 25% reduction if in expansion cohort, rounded down to the nearest tablet strength); monitor as clinically indicated.

Table 8: Guidelines for Interruption and Restarting of INCB057643 (Continued)

HEMATOLOGY			
Parameter	**Treatment Group/ Expansion Cohort**	**Adverse Event**	**Action Taken**
* ANC ($\times 10^9$/L)	Part 1/TGA; Part 3/C-ES-TGA/ TGB/TGC/TGD; Part 4/C-EX-TGA/ TGB	< 1.0	• Hold until resolved to ≥ 1.0; monitor CBC approximately every 3 days. • Restart INCB057643 at same dose and monitor; at second occurrence, restart INCB057643 at next lower dose and monitor.
		< 0.5	Discontinue INCB057643; consult medical monitor if needed.
	Parts 3/C-ES-TGE; Part 4/C-EX-TGC	≥ 50% decrease from baseline ANC count	• Evaluate underlying disease. • Consider dose interruption if cytopenias are NOT due to underlying disease or treatment with SOC agents. • Restart INCB057643 at next lower dose (or 25% reduction if in expansion cohort, rounded down to the nearest tablet strength); monitor as clinically indicated.
	Parts 1 and 2/TGB; Parts 3/C-ES-TGF; Part 4/C-EX-TGD	N/A	Neutropenia should be managed as per institutional standard, relevant to the underlying disease. Consult with the medical monitor for management outside of the institutional standard.
* Hgb (g/dL)	Part 1/TGA, Part 2/TGA; Part 1/TGC; Part 2/TGC; Part3 C-ES-TGA/ TGB/TGC/TGD; Part 4/C- EX-TGA/ TGB	< 8.0	• Hold until resolved to ≥ 8.0; monitor CBC approximately every 3 days; provide supportive care if needed. • Restart INCB057643 at same dose and monitor per Protocol. • At second occurrence, restart INCB057643 at next loser dose and monitor. • If recovery to > 8.0 does not occur within 14 days of dose interruption and/or is refractory to transfusion support, permanently discontinue INCB057643 and follow-up per protocol.
		< 6.5	Discontinue INCB057643; consult medical monitor if needed.
	Parts 1 and 2/TGB; Part 3/C-ES-TGE/ TGF; Part 4/C-EX-TGC/ TGD	N/A	Anemia should be managed as per institutional standard, relevant to the underlying disease. Consult with the medical monitor for management outside of institutional standard.

Table 8: Guidelines for Interruption and Restarting of INCB057643 (Continued)

CARDIAC MONITORING		
Event	**Grade**	**Action Taken**
Ejection fraction decreased (measured by either echocardiogram or MUGA)	Grade 2	• Mandatory hold of study treatment; may resume treatment at a reduced dose at the discretion of the investigator when ejection fraction recovered to > 50%; or discontinue treatment at the discretion of the investigator. • Mandatory discontinuation of treatment when recurred after resuming study treatment.
	Grade 3/4	• Mandatory discontinuation of treatment.
Cardiac troponin (either T or I)	Grade 1	• Mandatory hold of study treatment; may resume treatment at a reduced dose at the discretion of the investigator when cardiac troponin recovered within normal reference range; or discontinue treatment at the discretion of the investigator. • Mandatory discontinuation of treatment when recurred after resuming study treatment.
	Grade 3	• Mandatory discontinuation of treatment.

* Exceptions can be made for these hematologic toxicities without clinical consequence (eg, no fever, infection, bleeding).

5.4.3. Standard of Care Agent Dose Interruptions and Reductions

Action taken with any of the SOC combination agents in response to AEs should be in accordance with the respective agent's prescribing information and will be made at the discretion of the investigator; if needed, the sponsor's medical monitor should be consulted. Standard of care treatment cycles may be delayed, or the dose may be reduced for laboratory parameters or AEs that are judged by the investigator to be related to the SOC agent. If study drug needs to be permanently discontinued due to an AE clearly associated with the study drug, the SOC agent may be continued at the discretion of the investigator and with approval of the medical monitor.

5.4.3.1. Specific Guidelines for Gemcitabine and Paclitaxel in Solid Tumors

Specific guidelines for gemcitabine and paclitaxel dose interruptions, reductions, and modifications in the treatment of solid tumors is as follows:

1. Gemcitabine:
    a. Follow the label or institutional guidelines for dose interruption, restarting, and modification regarding hematologic toxicities.
    b. Generally, no dose modification is required for ≤ Grade 3 liver function test (LFT) abnormalities; discontinuation is required for Grade 4 LFT toxicity or Hy's Law cases.
    c. Generally, no dose modification is required for ≤ Grade 2 nonhematologic toxicities; dose reduction is recommended for Grade 3 AEs, and discontinuation is required for Grade 4 AEs.

2. Paclitaxel:
    a. Follow the label or institutional guidelines for dose interruption, restarting, and modification regarding hematologic toxicities.
    b. Dose interruption and reduction may be needed for ≥ Grade 2 neuropathy; discontinuation may be needed for persistent ≥ Grade 3 neuropathy.
    c. Generally, no dose modification is required for ≤ Grade 2 LFT abnormalities; 1-level dose reduction is recommended for concomitant Grade 2 ALT/AST elevation and Grade 1 total bilirubin increased, and 2-level dose reduction is recommended for Grade 3 LFT elevations. Discontinuation is required for Grade 4 LFT toxicity or Hy's Law cases.

5.4.4. Criteria for Permanent Discontinuation of INCB057643

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

- Occurrence of an AE that, 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.
- A persistent treatment-related AE requiring a delay of therapy for more than 2 weeks (14 days), unless a greater delay has been approved by the sponsor.
- An AE requiring more than 2 dose reductions of INCB057643, if below the PAD of INCB057643.

5.4.5. Criteria and Procedures for Dose Escalations of INCB057643

Intrasubject dose escalation of INCB057643 will be permitted in Part 1 and Part 3 with sponsor preapproval in the following circumstances:

- The Protocol eligibility criteria are met at the time of escalation.
- The subject has received ≥ 4 cycles of study drug without drug-related toxicity ≥ Grade 2.
- The dose level to which the subject will be escalating has been determined to be safe based on the MTD criteria.
- The subject is willing to submit to the PK, PD, and ECG schedule as required in Cycle 1 (other Cycle 1–specific assessments do not need to be repeated).
- In the opinion of the investigator, the subject does not have any concurrent condition or circumstance that would complicate the dose escalation or PK/PD sampling, or pose increased risk to the subject.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

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

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

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

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

5.5.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study drug, the last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the eCRF. In addition, the following steps should be followed (Note: These visits are described in Section 6):

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.
- The end of treatment (EOT) visit should be performed.
- The end of study (EOS) visit should be performed following the 30-day safety follow-up visit unless there is a going SAE or clinically significant AE. In this case, EOS visit will occur when the AE is resolved, returned to baseline, or deemed irreversible per the investigator.

- The date of the EOT visit should be recorded in the IRT.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, are deemed irreversible, or initiation of a new anticancer treatment, whichever occurs first.

5.6. Concomitant Medications

5.6.1. Restricted Medications

Restricted medications are as follows:

- Use of chronic systemic corticosteroid doses > 10 mg/day prednisone (or equivalent) is not permitted from screening through EOT, except for transient use of < 3 days. Short courses [≤ 3 days] of systemic corticosteroids > 10 mg/day prednisone (or equivalent) are permitted (eg, for transfusion reaction prophylaxis). Subjects with glioblastoma may be treated with corticosteroids (prednisone or equivalent) > 10 mg/day with approval from the medical monitor. Subjects receiving abiraterone may be treated with prednisone as per label instructions.
- Use of moderate inducers or inhibitors of CYP3A4 (see Appendix O) should be used with caution, and investigators should seek other options where possible.
  - Additional timed PK testing following the schedule for Cycle 1 Day 15 may be required if subjects initiate or require a dose adjustment of inhibitors or inducers of CYP3A4 during the study.
- Use of anticoagulants that will increase INR, such as coumarin-based anticoagulants (eg, warfarin), is discouraged, but not prohibited. Investigators are encouraged to switch subjects to alternate anticoagulation therapies which does not directly target Factor VII and increase INR. Coagulation panel should be monitored more closely while a subject is on any anticoagulant.
- Hydroxyurea for controlling proliferative disease is permitted with medical monitor approval, but should not be used within 48 hours before and on the day of PD sample collection or during or 72 hours before or after azacitidine administration.
- For subjects taking INCB057643 in combination with ruxolitinib only:
  - Aspirin in doses exceeding 125 mg/day is not permitted. Low-dose aspirin (≤ 125 mg/day) is permitted.
  - Caution should be used when administering ibuprofen or other nonsteroidal anti-inflammatory drugs with long elimination half-lives; subjects should be monitored closely for toxicity, especially for myelosuppression and renal and GI toxicity.

5.6.2. Prohibited Medications

Prohibited medications are as follows:

- Use of any anticancer drugs during study other than any Protocol-required agents. Denosumab and zoledronic acid are permitted to treat cancer-related bone diseases.
- Use of potent inducers and inhibitors of CYP3A4 (see Appendix O), with the exception of certain topical medications such as ketoconazole, based on its low overall bioavailability.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in Table 9, Table 11, Table 14, Table 17, Table 20, Table 23, and Table 26. All laboratory assessments will be performed as indicated in Table 10, Table 12, Table 15, Table 18, Table 21, Table 24, and Table 27. All timed PK assessments will be performed as indicated in Table 13, Table 16, Table 19, Table 22, Table 25, and Table 28. Table 30 described the laboratory analytes to be assessed. Section 7 describes the instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual.

For combination therapy treatment groups, Day 1 of each study cycle will correspond with the first day of SOC agent administration in that cycle; thus study cycles may become out of sync with the originally planned disease assessment schedule. **In this event, disease assessments will remain on the original schedule for that treatment group and will be measured from the baseline (screening) disease assessment.** All other assessments will shift to coincide with the revised treatment (cycle) schedule. For example, if one of the SOC agents has a delay in beginning therapy on Cycle 2 Day 1, the next scheduled visit when the SOC agent is administered will be Cycle 2 Day 1, and all other assessments will coincide with that Cycle 2 Day 1.

Table 9: Schedule of Assessments – Monotherapy INCB057643 (Part 1 and Part 2; All Treatment Groups)

Visit Day		Screening	Treatment							EOT	Disease Assessment	Safety Follow-Up
			C1				C2 and Beyond					
		D-28 to D-1	D1	D2	D8	D15	D1	D2[a]	D11[b]			
Evaluation/Window	Section				± 3 D	± 3 D	± 3 D		± 3 D	+ 3 D	Per Investigator Discretion	30 to 35 D After EOT
Informed consent	7.1	X										
Inclusion/exclusion criteria	3	X	X[c]									
Contact IRT	7.2	X	X				X			X		
Medical and cancer history	7.3	X										
Prior/concomitant medications	7.4	X[d]	X	X	X	X	X	X	X	X		X
AE assessment	7.5.1	X	X	X	X	X	X	X	X	X		X
Complete/targeted physical examination[e]	7.5.2	X[e]	X		X	X	X		X	X[e]		X[e]
ECOG performance status	7.6.1	X	X				X			X		X
Vital signs/weight	7.5.3	X	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X		X
12-Lead ECG	7.5.4	X					X					X
Timed triplicate 12-lead ECG[g]	7.5.4.3		X		X							
Immunophenotyping[h]	7.7.5	X	When confirming CR									
Tumor biopsy (TGA)[i]	7.7.4	X	Optional tumor biopsy during study, as clinically indicated									
Bone marrow examination (TGB and TGC)[j]	7.7.4	X					X[j]					
Buccal swab	7.9.10	X										
Efficacy/disease assessments[k]											X	
Skeletal survey[l]	7.7.8	X	At investigator discretion									
Administer INCB057643 in clinic	5.2.1.1		X	X	X		X[m]	X[m]				
Drug dispense/compliance check	5.2.1.4, 5.3		X				X			X[n]		
Provide reminder card	7.10.1	X	X	X	X	X	X	X	X	X		
Safety follow-up	6.4.1											X
Echocardiogram or MUGA	7.5.4.4		X				X			X		X

[a] Applicable to Part 2/TGA subjects in the food-effect study at Cycle 2 only. See Section 7.8.4 for details.
[b] After a subject has been on study for 6 months, Day 11 visits at subsequent cycles will be optional at the discretion of the investigator.
[c] On C1D1 only, review inclusion/exclusion criteria before dose administration.
[d] Prior medications documented only at screening.
[e] Comprehensive physical examination required at screening, EOT, and safety follow-up. Targeted physical examination will be conducted at other visits. Height will be measured at screening only.
[f] Weight not required.
[g] Triplicate ECGs will be performed predose and 0.5, 1, 2, 4, 6, and 8 hours postdose and within 15 minutes of the PK sampling on C1D1 and C1D8. Note that triplicate ECGs will be performed with a 1- to 3-minute break between evaluations.
[h] Immunophenotyping appropriate to the underlying pathology will be conducted by flow cytometry at screening and when confirming CR on subjects with lymphoma, leukemia, and MPNs (MDS/MPN and MF).

[i] All subjects in TGA (solid tumors and lymphoma) will have a tumor biopsy at screening (unless adequate archival tissue is available as per Section 7.9.9). This is not required for glioblastoma. Biopsy during treatment and/or at disease progression are strongly recommended, but not mandatory. For example, if a biopsy is performed during the treatment period to assess disease status, to confirm response or progression, or if otherwise clinically indicated, a sample of the biopsy will be provided to the sponsor. The subject will need to sign ICF for optional biopsy. See Section 7.9.9 for additional details.

[j] Investigators will perform disease and efficacy assessments per their own discretion. All subjects in TGB and TGC will have a bone marrow biopsy and/or aspirate (as appropriate to underlying pathology) at screening. For TGB, follow-up bone marrow biopsy and/or aspirates performed will be performed at Months 3, 6, 12, and yearly thereafter when required for response assessment, or as clinically indicated. For TGC, follow-up bone marrow biopsy for MM subjects will be performed if confirming a CR unless otherwise clinically indicated. For MDS/MPN and MF, follow-up bone marrow biopsy and/or aspirates performed will be performed at Months 3, 6, 12, and yearly thereafter when required for response assessment, or as clinically indicated. For AML subjects, bone marrow disease assessment during Cycle 2 is strongly recommended unless contraindicated. See Section 7.7.4 for additional details.

[k] Investigators will perform disease and efficacy assessments per their own discretion. Subjects in TGA will have efficacy/disease assessments performed every 9 weeks (± 1 week) during the treatment period. Subjects in TGB will have peripheral blood disease status assessments at screening, C1D1, C1D15, D1 of each subsequent cycle, and EOT. If screening assessments are performed within 7 days of treatment initiation, they do not need to be repeated at C1D1. Subjects with solid tumors, lymphoma, and MF will have imaging assessments every 9 weeks using the appropriate imaging modality (eg, MRI or CT for spleen/liver size assessment in MF). Bone marrow biopsy and/or aspirates performed as clinically indicated or at Months 3, 6, 12, and yearly thereafter when required for response assessment. See Section 7.7.4 for additional details. AML disease assessments will be performed on Day 1 of each cycle. Bone marrow biopsy and/or aspirates for response is to be performed at C4D1 or earlier as clinically indicated, followed by every other month as clinically indicated, or upon circulating blood cell recovery, to assess anti-leukemic activity (cytogenetic testing is not required if CR is not present). Note: For subjects who have a significant blast count reduction (as determined by the investigator) but have not completely cleared circulating blasts, the C4D1 bone marrow is still strongly encouraged to be performed to assess the impact of treatment on the bone marrow blast content. See Section 7.7.4 for additional details.

[l] TGC only.

[m] Applicable to Part 2/TGA subjects in the food-effect study at Cycle 2 only. See Section 7.8.4 for details.

[n] EOT visit – compliance check only.

Table 10: Schedule of Laboratory Assessments – Monotherapy INCB057643 (Part 1 and Part 2; All Treatment Groups)

Visit Day		Screening[a]	Treatment									
			C1				C2 and Beyond			Disease Assessment	EOT	Safety Follow-Up
		D-28 to D-1	D1	D2	D8	D15	D1	D2[b]	D11[c]			
Evaluation/Window	Section				± 3 D	± 3 D	± 3 D		± 3 D	Per Investigator Discretion	+ 3 D	30 to 35 D After EOT
Overnight fast before visit	7.8		X		X		X[b]					
Serum chemistry	7.5.5.1	X	X[d]	X	X	X	X		X		X	X
Hematology with differential	7.5.5.1	X	X[d]	X	X	X	X		X		X	X
Coagulation panel[e]	7.5.5.1	X[e]	X[d]	X	X[e]	X[e]	X[e]		X[e]		X	X
Factor VII protein antigen assay[e]	7.5.5.1	X[e]	X[d]		X[e]	X[e]	X[e]		X[e]		X	X
Urinalysis	7.5.5.1	X					X[f]				X	X
Lipid panel	7.5.5.1	X					X[f]				X	
Hepatitis testing	7.5.5.3	X										
Serum pregnancy test	7.5.5.2	X	X[g]								X	X
Timed PK – plasma[h]	7.8.1		X	X	X		X[b]	X[b]				
Timed PK – urine[i]	7.8.2				X							
Timed PD – plasma[j]	7.9.2		X	X	X							
[redacted]												
Cardiac troponin (T and/or I)	7.5.5.4		X				X				X	X

[a] Screening laboratory tests must be performed within 14 days before C1D1.
[b] Applicable to Part 2/TGA subjects in the food-effect study at Cycle 2 only. See Section 7.8.4 for details.
[c] After a subject has been on study for 6 months, Day 11 visits at subsequent cycles will be optional at the discretion of the investigator.
[d] If completed within 3 days before C1D1, this laboratory assessment may be omitted.
[e] All subjects will have coagulation panel conducted as indicated in the table and as needed. Extrinsic pathway coagulation factor profile, at minimum Factor VII protein/antigen assay concentration, will be obtained at screening or C1D1, C1D8, C1D15, C2D1, C2D11, and C3D1(sampling does not need to be repeated on Day 11 of Cycle 3 or any subsequent cycles). However, it should be performed any time there is a Grade 2 increased INR. If the last Factor VII result before the EOT visit is within normal range, Factor VII does not need to be tested EOT. If the Factor VII result at the EOT visit is within normal range, Factor VII does not need to be tested at the safety follow-up visit. Study visits do not need to be delayed waiting on the Factor VII protein/antigen assay results as long as INR/PT results are within normal limits.
[f] Urinalysis and lipid panel only performed at Cycles 2, 4, and 7 and every 3 cycles thereafter (eg, Cycle 10, Cycle 13, etc) during the treatment period.
[g] If the screening serum pregnancy test was completed within 3 days before C1D1, a urine pregnancy test may be performed.

[h] Collect timed PK samples predose (any time within 30 min of drug administration) and at 0.5 (± 5 min), 1 (± 15 min), 2 (± 15 min), 4 (± 15 min), 6 (± 30 min), and 8 (± 30 min) hours after administration on C1D1 and C1D8; C1D2 is predose only (any time within 30 min of drug administration).

[i] Predose void will be collected and time recorded from each subject. Total urine will be collected over an 8-hour interval after study drug administration. Two 10 mL aliquots will be collected. See Section 7.8.2 for details.

[j] Timed plasma PD will follow the same schedule as timed PK samples (predose [any time within 30 min of drug administration] and at 0.5 [± 5 min], 1 [± 15 min], 2 [± 15 min], 4 [± 15 min], 6 [± 30 min], and 8 [± 30 min] hours after administration on C1D1 and C1D8; C1D2 is predose only [any time within 30 min of drug administration]).

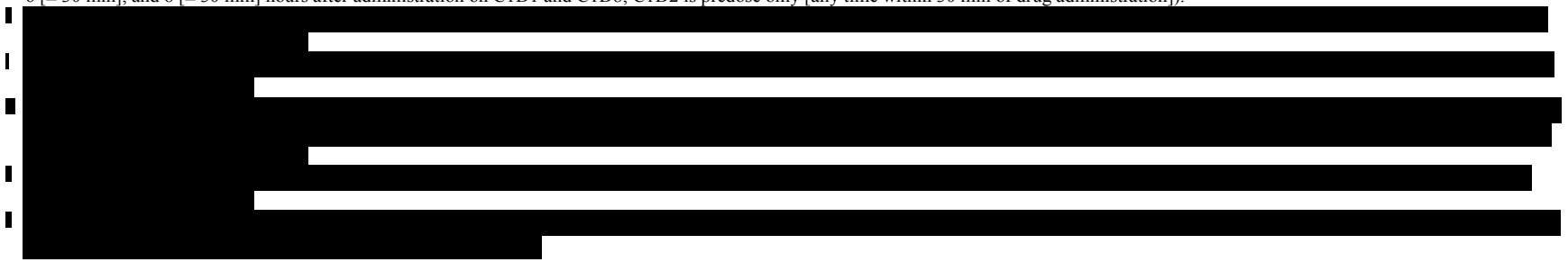


Table 11: Schedule of Assessments – Combination INCB057643 and Gemcitabine (Part 3 C-ES-TGA)

			Treatment							
		Screening	C1 and C2			C3 and Beyond		Disease Assessment	EOT	Safety Follow-Up
Visit Day		**D-28 to D-1**	**D1**	**D8**	**D15**	**D1**	**D8**			
Evaluation/Window	**Section**		**± 3 D (C2D1 only)**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**Per Investigator Discretion**	**+ 3 D**	**30 to 35 D After EOT**
Informed consent	7.1	X								
Inclusion/exclusion criteria	3	X	X[a]							
Contact IRT	7.2	X	X			X			X	
Medical and cancer history	7.3	X								
Prior/concomitant medications	7.4	X[b]	X	X	X	X	X		X	X
AE assessment	7.5	X	X	X	X	X	X		X	X
Complete/targeted physical examination[c]	7.5.2	X[c]	X	X	X	X	X		X[c]	X
ECOG performance status	7.6.1	X	X			X			X	X
Vital signs/weight	7.5.3	X	X[d]	X	X	X[d]	X		X	X
12-Lead ECG[e]	7.5.4.1	X	X			X			X	
Tumor biopsy[f]	7.7.3	X	Optional tumor biopsy during the treatment period and/or at EOT/disease progression, or as clinically indicated.							
Buccal swab	7.9.10	X								
Disease assessments[g]	7.7	X						X	X	
Administer INCB057643 in clinic[h]	5.2.1.1		X	X		X				
Administer gemcitabine in clinic[i]	5.2.2.1		X	X		X	X			
Drug dispense/compliance check[j]	5.2.1.4, 5.3		X	X	X	X	X		X	
Provide reminder card	7.10.1	X	X	X	X	X	X		X	X
Safety follow-up	6.4.1									X
Echocardiogram or MUGA	7.5.4.4		X			X			X	X

[a] On C1D1 only, review inclusion/exclusion criteria before dose administration.
[b] Prior medications documented only at screening.
[c] Complete physical examination at screening and EOT only. Height at screening only. Targeted physical examination all other visits.
[d] Weight is measured on Day 1 of each cycle only.
[e] All 12-lead ECGs will be performed with the subject in a recumbent or semi-recumbent position after 5 minutes of rest and will not be performed within 15 minutes after a blood collection. Electrocardiograms may be performed throughout treatment as clinically indicated.
[f] Tumor biopsy at screening is required; tumor biopsy during the treatment period and/or at disease progression is strongly recommended but not mandatory.
[g] The same imaging technique will be used in a subject throughout the study.
[h] INCB057643 will be administered in the clinic for any study visit where a PK sample is drawn and on Day 1 of each cycle. INCB057643 will be administered before chemotherapy.
[i] Gemcitabine will be administered on Days 1 and 8 of each 21-day cycle. Subjects may receive prophylactic G-CSF support with filgrastim (Neupogen) per institutional guidelines, however, it will not be given in the first cycle unless discussed with the medical monitor. Dosing delay, interruption, reduction, or termination is allowed for AE management.
[j] Dispense study drug on Day 1 of each cycle; on all other days, compliance check is required.

Table 12: Schedule of Laboratory Assessments – Combination INCB057643 and Gemcitabine (Part 3 C-ES-TGA)

Visit Day	Section	Screening[a]	Treatment					Disease Assessment	EOT	Safety Follow-Up
			C1 and C2			C3 and Beyond				
		D-28 to D-1	D1	D8	D15	D1	D8			
Evaluation Window			± 3 D (C2D1 only)	± 3 D	± 3 D	± 3 D	± 3 D	Per Investigator Discretion	+ 3 D	30 to 35 D After EOT
Overnight fast before visit	7.8		X[b]	X[b]						
Serum chemistry	7.5.5.1	X	X[c]	X	X	X	X		X	X
Hematology with differential	7.5.5.1	X	X[c]	X	X	X	X		X	X
Coagulation panel[d]	7.5.5.1	X	X[c]	X	X	X			X	X
Factor VII protein/antigen assay[d]	7.5.5.1	X	X[c]	X	X	X			X	X
Urinalysis[e]	7.5.5.1	X	X[e]			X[e]			X	X
Lipid panel[e]	7.5.5.1	X	X[e]			X[e]			X	
Hepatitis testing	7.5.5.3	X								
Serum pregnancy test	7.5.5.2	X	X[f]						X	X
[redacted]										
Cardiac troponin (either T or I)	7.5.5.4		X			X			X	X

[a] Screening laboratory tests must be performed within 14 days before C1D1.
[b] Only required during Cycle 1.
[c] If completed within 3 days before C1D1, this laboratory assessment may be omitted.
[d] All subjects will have coagulation panel conducted at screening, C1D1, C1D8, C1D15, C2D1, C2D8, Day 1 of each subsequent cycle, and when clinically indicated. If a subject is on a coumarin-based anticoagulant, such as warfarin, in addition to required testing per Protocol, coagulation panel may be tested as per standard of care or at the investigator's discretion. Extrinsic pathway coagulation factor profile, at minimum Factor VII protein/antigen assay concentration, will be obtained at screening or C1D1, C1D8, C1D15, C2D1, C2D8, C3D1, and any time there is a Grade 2 increased INR along with the coagulation panel. If the last Factor VII result before the EOT visit is within normal range, Factor VII does not need to be tested at EOT. If the Factor VII result at the EOT visit is within normal range, Factor VII does not need to be tested at the safety follow-up visit. Study visits do not need to be delayed waiting on the Factor VII results as long as INR/PT results are eligible according to enrollment eligibility. Factor VII does not need to extend beyond C3D1.
[e] Urinalysis and lipid panel only performed at Cycles 2, 4, and 7 and every 3 cycles thereafter (eg, Cycle 10, Cycle 13, etc) during the treatment period.
[f] If the screening serum pregnancy test was completed within 3 days before C1D1, a urine pregnancy test may be performed.
[g] Correlative plasma will be collected predose C1D1, C2D1, at each disease assessment, and at EOT. Refer to the Laboratory Manual for collection methods. May be drawn after the subject signs the ICF, is approved for enrollment, and within 7 days before dose administration on C1D1.

[redacted]

Table 13: Schedule of Timed Pharmacokinetic Assessments – Combination INCB057643 and Gemcitabine (Part 3 C-ES-TGA)

Visit	Fasting Requirement	HOLD AM Dose	Predose[a]	INCB057643 Dose[b]	Gemcitabine Dose	Time Postdose[a]					
						1 h ± 15 min	Snack or Meal	2 h ± 15 min	4 h ± 15 min	6 h ± 15 min	8 h ± 30 min
C1D1	At least 8 h before study drugs	N/A	X	♦	♦	X	X	X	X	X	X
C1D8	At least 8 h before study drugs	X	X	♦	♦	X	X	X	X	X	X

[a] Collect timed PK samples predose (any time within 30 min of INCB057643 administration) and at 1 (± 15 min), 2 (± 15 min), 4 (± 15 min), 6 (± 30 min), and 8 (± 30 min) hours after INCB057643 administration on C1D1 and C1D8.
[b] INCB057643 dose will be administered just before the dose of gemcitabine.

Table 14: Schedule of Assessments – Combination INCB057643 and Paclitaxel (Part 3 C-ES-TGB)

Visit Day		Screening	Treatment						Disease Assessment	EOT	Safety Follow-Up
			C1 and C2			C3 and Beyond					
		D-28 to D-1	D1	D8	D15	D1	D8	D15			
Evaluation Window	**Section**		**± 3 D (C2D1 only)**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**Per Investigator Discretion**	**+ 3 D**	**30 to 35 D After EOT**
Informed consent	7.1	X									
Inclusion/exclusion criteria	3	X	X[a]								
Contact IRT	7.2	X	X			X				X	
Medical and cancer history	7.3	X									
Prior/concomitant medications	7.4	X[b]	X	X	X	X	X	X		X	X
AE assessment	7.5	X	X	X	X	X	X	X		X	X
Complete/targeted physical examination[c]	7.5.2	X[c]	X	X	X	X	X	X		X	X
ECOG performance status	7.6.1	X	X			X				X	X
Vital signs/weight	7.5.3	X	X[d]	X	X	X[d]	X	X		X	X
12-Lead ECG[e]	7.5.4.1	X	X			X				X	
Tumor biopsy[f]	7.7.3	X	Optional tumor biopsy during the treatment period and/or at EOT/disease progression, or as clinically indicated.								
Buccal swab	7.9.10	X									
Disease assessments[g]	7.7	X							X	X	
Administer INCB057643 in clinic[h]	5.2.1.1		X	X		X					
Administer paclitaxel in clinic[i]	5.2.2.2		X	X	X	X	X	X			
Drug dispense/compliance check[j]	5.2.1.4, 5.3		X	X	X	X	X	X		X	
Provide reminder card	7.10.1	X	X	X	X	X	X	X		X	X
Safety follow-up	6.4.1										X
Echocardiogram or MUGA	7.5.4.4		X			X				X	X

[a] On C1D1 only, review inclusion/exclusion criteria before dose administration.
[b] Prior medications documented only at screening.
[c] Complete physical examination at screening only. Height at screening only. Targeted physical examination at all other visits.
[d] Weight is measured on Day 1 of each cycle only.
[e] All 12-lead ECGs will be performed with the subject in a recumbent or semi-recumbent position after 5 minutes of rest and will not be performed within 15 minutes after a blood collection. Electrocardiograms may be performed throughout treatment as clinically indicated.
[f] Tumor biopsy at screening is required; tumor biopsy during treatment and/or at disease progression is strongly recommended but not mandatory.
[g] The same imaging technique will be used in a subject throughout the study.
[h] INCB057643 will be administered in the clinic for any study visit where a PK sample is drawn and on Day 1 of each cycle. INCB057643 will be administered before chemotherapy.
[i] Paclitaxel will be administered on Days 1, 8, and 15 of each 21-day cycle. Subjects must receive premedications (IV or PO) with corticosteroids, H1- and H2-antagonists, antihistamine, and antiemetics based on institutional guidelines, investigator practice, or local prescribing information or standards of care. Subjects may receive prophylactic G-CSF support with filgrastim (Neupogen) per institutional guidelines. Prophylactic G-CSF will not be given in the first cycle unless discussed with the medical monitor. Dosing delay, interruption, reduction, or termination is allowed for AE management.
[j] Dispense study drug on Day 1 of each cycle; on all other days, compliance check is required.

Table 15: Schedule of Laboratory Assessments – Combination INCB057643 and Paclitaxel (Part 3 C-ES-TGB)

Visit Day	Section	Screening[a]	Treatment						Disease Assessment	EOT	Safety Follow-Up
			C1 and C2			C3 and Beyond					
		D-28 to D-1	D1	D8	D15	D1	D8	D15			
Evaluation Window			± 3 D (C2D1 only)	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	Per Investigator Discretion	+3 D	30 to 35 D After EOT
Overnight fast before visit[b]	7.8		X	X							
Serum chemistry	7.5.5.1	X	X[c]	X	X	X	X	X		X	X
Hematology with differential	7.5.5.1	X	X[c]	X	X	X	X	X		X	X
Coagulation panel[d]	7.5.5.1	X	X[c]	X	X	X				X	X
Factor VII protein/antigen assay[d]	7.5.5.1	X	X[c]	X	X	X				X	X
Urinalysis[e]	7.5.5.1	X	X[e]			X[e]				X	X
Lipid panel[e]	7.5.5.1	X	X[e]			X[e]				X	
Hepatitis testing	7.5.5.3	X									
Serum pregnancy test	7.5.5.2	X	X[f]							X	X
[redacted]											
Cardiac troponin (either T or I)	7.5.5.4		X			X				X	X

[a] Screening laboratory tests must be performed within 14 days before C1D1.
[b] Only required during Cycle 1.
[c] If completed within 3 days before C1D1, this laboratory assessment may be omitted.
[d] All subjects will have coagulation panel including Factor VII protein/antigen assay concentration conducted at screening, C1D1, C1D8, C1D15, C2D1, C2D8, C2D15, C3D1, and any time there is a Grade 2 increased INR. If the last Factor VII result before the EOT visit is within normal range, Factor VII does not need to be tested at EOT. If the Factor VII result at the EOT visit is within normal range, Factor VII does not need to be tested at the safety follow-up visit. If a subject is on a coumarin-based anticoagulant, such as warfarin, in addition to required testing per Protocol, coagulation panel may be tested as per standard of care or at the investigator's discretion. Study visits do not need to be delayed waiting on the Factor VII results as long as INR/PT results are eligible according to enrollment eligibility. Factor VII does not need to extend beyond C3D1. Coagulation panel is conducted on Day 1 of each subsequent cycle beginning with Cycle 3.
[e] Urinalysis and lipid panel only performed at Cycles 2, 4, and 7 and every 3 cycles there after (eg, Cycle 10, Cycle 13, etc) during the treatment period.
[f] If the screening serum pregnancy test was completed within 3 days before C1D1, a urine pregnancy test may be performed.
[redacted]

Table 16: Schedule of Timed Pharmacokinetic Assessments – Combination INCB057643 and Paclitaxel (Part 3 C-ES-TGB)

Visit	Fasting Requirement	HOLD AM Dose	Predose[a]	INCB057643 Dose[b]	Paclitaxel Dose	Time Postdose[a]					
						1 h ± 15 min	Snack or Meal	2 h ± 15 min	4 h ± 15 min	6 h ± 15 min	8 h ± 30 min
C1D1	At least 8 h before the study drugs	N/A	X	♦	♦	X	X	X	X	X	X
C1D8	At least 8 h before the study drugs	X	X	♦	♦	X	X	X	X	X	X

[a] Collect timed PK samples predose (any time within 30 min of INCB057643 administration) and at 1 (± 15 min), 2 (± 15 min), 4 (± 15 min), 6 (± 30 min), and 8 (± 30 min) hours after INCB057643 administration on C1D1 and C1D8.
[b] INCB057643 dose will be administered just before the daily dose of paclitaxel.

Table 17: Schedule of Assessments – Combination INCB057643 and Rucaparib (Part 3 C-ES-TGC and Part 4 C-EX-TGA)

Visit Day		Screening	Treatment							
			C1			C2 and Beyond		Disease Assessment	EOT	Safety Follow-Up
		D-28 to D-1	D1	D8	D15	D1	D11[a]			
Evaluation Window	**Section**			± 3 D	± 3 D	± 3 D	± 3 D	Per Investigator Discretion	+ 3 D	30 to 35 D After EOT
Informed consent	7.1	X								
Inclusion/exclusion criteria	3	X	X[b]							
Contact IRT	7.2	X	X			X			X	X
Medical and cancer history	7.3	X								
Prior/concomitant medications	7.4	X[c]	X	X	X	X	X		X	X
AE assessment	7.5	X	X	X	X	X	X		X	X
ECOG performance status	7.6.1	X	X			X			X	X
Comprehensive/targeted physical examination[d]	7.5.2	X[d]	X	X	X	X	X		X	X
Vital signs/weight[e]	7.5.3	X	X[e]	X	X	X[e]	X		X	X
12-Lead ECG[f]	7.5.4.1	X	X			X			X	X
Buccal swab	7.9.10	X								
Tumor biopsy[g]	7.7.3	X				Optional tumor biopsy during the treatment period and/or at EOT/disease progression, or as clinically indicated.				
Disease assessments[h]	7.7	X						X	X	
Administer INCB057643 in clinic[i]	5.2.1.1		X	X		X				
Administer rucaparib in clinic[j]	5.2.2.3		X	X		X				
Drug dispense/compliance check[k]	5.2.1.4, 5.3		X[k]	X	X	X[k]	X		X	
Provide reminder card	7.10.1	X	X	X	X	X	X		X	
Safety follow-up	6.4.1									X
Echocardiogram or MUGA	7.5.4.4		X			X			X	X

[a] After a subject has been on study for 6 months, Day 11 visits at subsequent cycles will be optional at the discretion of the investigator.
[b] On C1D1 only, review inclusion/exclusion criteria before dose administration.
[c] Prior medications documented only at screening.
[d] Complete physical examination at screening only. Height at screening only. Targeted physical examination at all other visits.
[e] Weight is measured on Day 1 of each cycle.
[f] All 12-lead ECGs will be performed with the subject in a recumbent or semi-recumbent position after 5 minutes of rest and will not be performed within 15 minutes after a blood collection. Electrocardiograms may be performed throughout treatment as clinically indicated.
[g] Tumor biopsy at screening is required; tumor biopsy during treatment and/or at disease progression are strongly recommended but not mandatory.
[h] The same imaging technique will be used in a subject throughout the study.
[i] INCB057643 will be administered in the clinic for any study visit where a PK sample is drawn and on Day 1 of each cycle. INCB057643 will be administered before rucaparib.
[j] Rucaparib will be administered in the clinic for any study visit where a PK sample is drawn and on Day 1 of each cycle.
[k] Dispense drug on Day 1 of each cycle; on all other days, compliance check is required.

Table 18: Schedule of Laboratory Assessments – Combination INCB057643 and Rucaparib (Part 3 C-ES-TGC and Part 4 C-EX-TGA)

Visit Day	Section	Screening[a]	Treatment					Disease Assessment	EOT	Safety Follow-Up
			C1			C2 and Beyond				
		D-28 to D-1	D1	D8	D15	D1	D11[b]			
Evaluation Window				± 3 D	± 3 D	± 3 D	± 3 D	Per Investigator Discretion	+ 3 D	30 to 35 D After EOT
Overnight fast before visit[c]	7.8		X	X						
Serum chemistry	7.5.5.1	X	X[d]	X	X	X	X		X	X
Hematology with differential	7.5.5.1	X	X[d]	X	X	X	X		X	X
Coagulation panel[e]	7.5.5.1	X	X[d]	X	X	X			X	X
Factor VII protein/antigen assay[e]	7.5.5.1	X	X[d]	X	X	X			X	X
Urinalysis[f]	7.5.5.1	X				X[f]			X	X
Lipid panel[f]	7.5.5.1	X				X[f]			X	
Hepatitis testing	7.5.5.3	X								
Serum pregnancy test	7.5.5.2	X	X[g]						X	X
[redacted]										
Cardiac troponin (either T or I)	7.5.5.4		X			X			X	X

[a] Screening laboratory tests must be performed within 14 days before C1D1.
[b] After a subject has been on study for 6 months, Day 11 visits at subsequent cycles will be optional at the discretion of the investigator.
[c] Only required for Cycle 1.
[d] If completed within 3 days before C1D1, this laboratory assessment may be omitted.
[e] All subjects will have coagulation panel including Factor VII protein/antigen assay concentration conducted at screening, C1D1, C1D8, and C1D15. Subsequently, Factor VII only needs to be collected on Day 1 of Cycle 2 and Cycle 3; coagulation panel is conducted on Day 1 of each subsequent cycle beginning with Cycle 2. Factor VII protein/antigen assay will also be collected upon a Grade 2 increased INR. If the last Factor VII result before the EOT visit is within normal ranger, Factor VII does not need to be tested at EOT. If the Factor VII result at the EOT visit is within normal range, Factor VII does not need to be tested at the safety follow-up visit. If a subject is on a coumarin-based anticoagulant, such as warfarin, in addition to required testing per Protocol, coagulation panel may be tested as per standard of care or at the investigator's discretion. Study visits do not need to be delayed waiting on the Factor VII results as long as INR/PT results are eligible according to enrollment eligibility.
[f] Urinalysis and lipid panel only performed at Cycles 2, 4, and 7 and every 3 cycles there after (eg, Cycle 10, Cycle 13, etc) during the treatment period.
[g] If the screening serum pregnancy test was completed within 3 days before C1D1, a urine pregnancy test may be performed.
[redacted]

Table 19: Schedule of Timed Pharmacokinetic Assessments – Combination INCB057643 and Rucaparib (Part 3 C-ES-TGC and Part 4 C-EX-TGA)

Visit	Fasting Requirement	HOLD AM Dose	Predose[a]	INCB057643 Dose[b]	Rucaparib Dose	Time Postdose[a]						
						0.5 h ± 15 min	1 h ± 15 min	Snack or Meal	2 h ± 15 min	4 h ± 15 min	6 h ± 15 min	8 h ± 30 min
C1D1	At least 8 h before the study drugs	N/A	X	♦	♦	X	X	X	X	X	X	X
C1D8	At least 8 h before the study drugs	X	X	♦	♦	X	X	X	X	X	X	X

[a] Collect timed PK samples predose (any time within 30 min of INCB057643 administration) and at 0.5 (± 5 min), 1 (± 15 min), 2 (± 15 min), 4 (± 15 min), 6 (± 30 min), and 8 (± 30 min) hours after INCB057643 administration on C1D1 and C1D8.
[b] INCB057643 dose will be administered just before the dose of rucaparib.

Table 20: Schedule of Assessments – Combination INCB057643 and Abiraterone (Part 3 C-ES-TGD and Part 4 C-EX-TGB)

Visit Day		Screening	Treatment					Disease Assessment	EOT	Safety Follow-Up
			C1			C2 and Beyond				
		D-28 to D-1	D1	D8	D15	D1	D11[a]			
Evaluation Window	**Section**			± 3 D	± 3 D	± 3 D	± 3 D	**Per Investigator Discretion**	+ 3 D	**30 to 35 D After EOT**
Informed consent	7.1	X								X
Inclusion/exclusion criteria	3	X	X[b]							
Contact IRT	7.2	X	X			X			X	
Medical and cancer history	7.3	X								
Prior/concomitant medications	7.4	X[c]	X	X	X	X	X		X	X
AE assessment	7.5	X	X	X	X	X	X		X	X
Complete/targeted physical examination[d]	7.5.2	X[d]	X	X	X	X	X		X	X
ECOG performance status	7.6.1	X	X			X			X	X
Vital signs/weight[e]	7.5.3	X	X[e]	X	X	X[e]	X		X	X
12-lead ECG[f]	7.5.4.1	X	X			X			X	
Tumor biopsy[g]	7.7.3	X				Optional tumor biopsy during the treatment period and/or at EOT/disease progression, or as clinically indicated.				
Buccal swab	7.9.10	X								
Disease assessments: imaging (nodal, visceral, and bone)[h]	7.7.10	X						X	X	
Disease assessments: blood-based PSA[i]	7.7.10	X				X		X	X	
Administer INCB057643 in clinic[j]	5.2.1.1		X	X		X				
Administer abiraterone in clinic[k]	5.2.2.4		X	X		X				
Drug dispense/compliance check[l]	5.2.1.4, 5.3		X	X	X	X	X		X	
Provide reminder card	7.10.1	X	X	X	X	X	X		X	X
Safety follow-up	6.4.1									X
Echocardiogram or MUGA	7.5.4.4		X			X			X	X

[a] After a subject has been on study for 6 months, Day 11 visits at subsequent cycles will be optional at the discretion of the investigator.
[b] On C1D1 only; review inclusion/exclusion criteria before dosing dose administration.
[c] Prior medications are only documented at screening.
[d] Complete physical examination at screening only. Height at screening only. Targeted physical examination at all other visits.
[e] Weight is measured on Day 1 of each cycle.
[f] All 12-lead ECGs will be performed with the subject in a recumbent or semi-recumbent position after 5 minutes of rest and will not be performed within 15 minutes after a blood collection. Electrocardiograms may be performed throughout treatment as clinically indicated.
[g] Tumor biopsy at screening is required; tumor biopsy during treatment and/or at disease progression is strongly recommended but not mandatory.
[h] Investigators will perform disease and efficacy assessments per their own discretion. The same imaging technique will be used in a subject throughout the study.
[i] Blood-based PSA will be assessed at screening, C2D1, Day 1 of each subsequent cycle, at the time of imaging disease assessment, and when clinically indicated.

[j] INCB057643 and abiraterone will be administered in the clinic for any study visit where a PK sample is drawn. INCB057643 will be administered before chemotherapy.
[k] Abiraterone will be administered orally QD with two 500 mg tablets or four 250 mg tablets in combination with prednisone 5 mg administered orally BID (continuous dosing). Abiraterone will be taken on an empty stomach. No food will be consumed for at least 2 hours before the dose is taken and for at least 1 hour after the dose is taken in a 21-day cycle.
[l] Dispense drug on Day1 of each cycle; at all other visits, compliance check is required.

Table 21: Schedule of Laboratory Assessments – Combination INCB057643 and Abiraterone (Part 3 C-ES-TGD and Part 4 C-EX-TGB)

Visit Day		Screening[a]	Treatment					Disease Assessment	EOT	Safety Follow-Up
			C1			C2 and Beyond				
		D-28 to D-1	D1	D8	D15	D1	D11[b]			
Evaluation Window	Section			± 3 D	± 3 D	± 3 D	± 3 D	Per Investigator Discretion	+ 3 D	30 to 35 D After EOT
Overnight fast before visit	7.8		X	X						
Serum chemistry	7.5.5.1	X	X[c]	X	X	X	X		X	X
Hematology with differential	7.5.5.1	X	X[c]	X	X	X	X		X	X
Coagulation panel[d]	7.5.5.1	X	X[c]	X	X	X			X	X
Factor VII protein/antigen assay[d]	7.5.5.1	X	X[c]	X	X	X			X	X
Urinalysis[e]	7.5.5.1	X				X[e]			X	X
Lipid panel[e]	7.5.5.1	X				X[e]			X	
Hepatitis testing	7.5.5.3	X								
Serum pregnancy test	7.5.5.2	X	X[f]						X	X
[redacted]										
Cardiac troponin (either T or I)	7.5.5.4		X			X			X	X

[a] Screening laboratory tests must be performed within 14 days before C1D1.
[b] After a subject has been on study for 6 months, Day 11 visits at subsequent cycles will be optional at the discretion of the investigator.
[c] If completed within 3 days before C1D1, this laboratory assessment may be omitted.
[d] All subjects will have coagulation panel including Factor VII protein/antigen assay concentration conducted at screening, C1D1, C1D8, C1D15. Subsequently, Factor VII only needs to be collected on Day 1 of Cycle 2 and Cycle 3. Coagulation panel is conducted on Day 1 of each subsequent cycle beginning with Cycle 2. Factor VII protein/antigen assay will also be collected upon a Grade 2 increased INR. If the last Factor VII result before the EOT visit is within normal range, Factor VII does not need to be tested at EOT. If the Factor VII result at the EOT visit is within normal range, Factor VII does not need to be tested at the safety follow-up visit. If a subject is on a coumarin-based anticoagulant, such as warfarin, in addition to required testing per protocol, coagulation panel may be tested as per standard of care or at the investigator's discretion. Study visits do not need to be delayed waiting on the Factor VII results as long as INR/PT results are eligible according to enrollment eligibility.
[e] Urinalysis and lipid panel only performed at Cycles 2, 4, and 7 and every 3 cycles there after (eg, Cycle 10, Cycle 13, etc) during the treatment period.
[f] If the screening serum pregnancy test was completed within 3 days before C1D1, a urine pregnancy test may be performed.
[redacted]

Table 22: Schedule of Timed Pharmacokinetic Assessments – Combination INCB057643 and Abiraterone (Part 3 C-ES-TGD and Part 4 C-EX-TGB)

Visit	Fasting Requirement	HOLD AM Dose	Predose[a]	INCB057643 Dose[b]	Abiraterone Dose	Time Postdose[a]						
						0.5 h ± 15 min	1 h ± 15 min	Snack or Meal	2 h ± 15 min	4 h ± 15 min	6 h ± 15 min	8 h ± 30 min
C1D1	At least 8 h before the study drugs	N/A	X	♦	♦	X	X	X	X	X	X	X
C1D8	At least 8 h before the study drugs	X	X	♦	♦	X	X	X	X	X	X	X

[a] Collect timed PK samples predose (any time within 30 min of INCB057643 administration) and at 0.5 (± 5 min), 1 (± 15 min), 2 (± 15 min), 4 (± 15 min), 6 (± 30 min), and 8 (± 30 min) hours after INCB057643 administration on C1D1 and C1D8.
[b] INCB057643 dose will be administered just before the dose of abiraterone.

Table 23: Schedule of Assessments – Combination INCB057643 and Ruxolitinib (Part 3 C-ES-TGE and Part 4 C-EX-TGC)

Visit Day		Screening	Treatment					Disease Assessment	EOT	Safety Follow-Up
			C1			C2 and Beyond				
		D-28 to D-1	D1	D8	D15	D1	D11[a]			
Evaluation Window	**Section**			**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**Per Investigator Discretion**	**+ 3 D**	**30 to 35 D After EOT**
Informed consent	7.1	X								
Inclusion/exclusion	3	X	X[b]							
Contact IRT	7.2	X	X			X			X	
Medical and cancer history	7.3	X								
Prior/concomitant medications	7.4	X[c]	X	X	X	X	X		X	X
Transfusion history/status	7.3.1	X	X[d]			X[d]			X	X
Screening Symptom Form	7.3.2	X								
Administer INCB057643 in clinic	5.2.1.1		X	X		X				
Administer ruxolitinib in clinic	5.2.2.5		X	X		X				
Drug dispense/compliance check[e]	5.2.1.4, 5.3		X	X	X	X	X		X	
Complete physical examination	7.5.2.1	X[f]							X	X
Targeted physical examination	7.5.2.2		X	X	X	X	X			
Spleen palpation	7.7.9	X	X[g]			X[g]			X	X
ECOG performance status	7.6.1	X	X[g]			X[g]			X	X
Vital signs/weight[h]	7.5.3	X[h]	X	X	X	X	X		X	X
12-lead ECG	7.5.4.1	X	X			X[i]			X	X
AE assessment	7.5	X	X	X	X	X	X		X	X
Buccal swab	7.9.10	X								
Bone marrow[j]	7.7.4	X						X		
MRI/CT Scan of abdomen/pelvis	7.7.1	X						X[k]		
IWG-MRT assessment[l]	7.7.4, Appendix H							X	X	
Provide reminder card	7.10.1	X	X	X	X	X	X		X	
Safety follow-up	6.4.1									X
Echocardiogram or MUGA	7.5.4.4		X			X			X	X

[a] After a subject has been on study for 6 months, Day 11 visits at subsequent cycles will be optional at the discretion of the investigator.
[b] On C1D1 only, review inclusion/exclusion criteria before dose administration.
[c] Prior medications are collected only at screening.
[d] Transfusion history/status will be conducted on Day 1 of each cycle through Cycle 8; then Day 1 of every 4th cycle thereafter.
[e] Drug will be dispensed on Day 1 of each cycle. Drug compliance will be checked at each visit.
[f] Height at screening only.
[g] Spleen palpation and ECOG assessment will be conducted on Day 1 of each cycle through Cycle 8; then Day 1 of every 4th cycle thereafter.

[h] Weight will be checked at each visit along with vital signs.
[i] Starting at Cycle 4 and continuing every 12 weeks thereafter.
[j] Investigators will perform disease and efficacy assessments per their own discretion. Bone marrow biopsy must be completed at screening, unless biopsy and data from previous 2 months are available. Additional biopsies will be performed at Week 24, Week 48, and every 24 weeks thereafter. If a biopsy is not possible or contraindicated, or the tissue requirement cannot be satisfied, this requirement may be waived with approval from the medical monitor.
[k] Through Week 108.
[l] The first IWG-MRT assessment will be conducted at Week 24 and then every 12 weeks thereafter.**Error! Reference source not found.**

Table 24: Schedule of Laboratory Assessments – Combination INCB057643 and Ruxolitinib (Part 3 C-ES-TGE and Part 4 C-EX-TGC)

Visit Day		Screening[a]	Treatment							
			C1			C2 and Beyond		Disease Assessment	EOT	Safety Follow-Up
		D-28 to D-1	D1	D8	D15	D1	D11[b]			
Evaluation Window	**Section**			**± 3 D**	**± 3 D**	**± 3 D**	**± 3 D**	**Per Investigator Discretion**	**+ 3 D**	**30 to 35 D After EOT**
Overnight fast before visit	7.8		X	X		X				
Serum chemistry	7.5.5.1	X	X[c]	X	X	X	X		X	X
Hematology with differential	7.5.5.1	X	X[c]	X	X	X	X		X	X
Coagulation panel[d]	7.5.5.1	X	X[c]	X	X	X	X		X	X
Factor VII protein/antigen assay[d]	7.5.5.1	X	X[c]	X	X	X	X		X	X
Urinalysis[e]	7.5.5.1	X				X[e]			X	X
Lipid panel (requires overnight fast for Part 3 only)[e]	7.5.5.3		X			X[e]			X	
Hepatitis testing	7.5.5.2	X								
Serum pregnancy test	7.5.5.2	X	X[f]						X	X
[redacted]										
Cardiac troponin (either T or I)	7.5.5.4		X			X			X	X

[a] Screening laboratory tests must be performed within 14 days before C1D1.
[b] After a subject has been on study for 6 months, Day 11 visits at subsequent cycles will be optional at the discretion of the investigator.
[c] If completed within 3 days before C1D1, this laboratory assessment may be omitted.
[d] All subjects will have coagulation panel including Factor VII protein concentration by the Factor VII antigen assay conducted at screening, C1D1, C1D8, C1D15, C2D1, C2D11, and C3D1. Coagulation panel is conducted on Day 1 of each subsequent cycle beginning with Cycle 4, more frequent if clinically indicated. Factor VII protein/antigen assay will also be collected upon a Grade 2 increased INR, or if clinically indicated. If the last Factor VII result before the EOT visit is within normal range, Factor VII does not need to be tested at EOT. If the Factor VII result at the EOT visit is within normal range, Factor VII does not need to be tested at the safety follow-up visit. If a subject is on a coumarin-based anticoagulant, such as warfarin, in addition to required testing per Protocol, coagulation panel may be tested as per standard of care or at the investigator's discretion. Study visits do not need to be delayed waiting on the Factor VII results as long as INR/PT results are eligible according to enrollment eligibility.
[e] Urinalysis and lipid panel only performed at Cycles 2, 4, and 7 and every 3 cycles there after (eg, Cycle 10, Cycle 13, etc). For Part 3, subjects will have fasting lipid panels at C1D1; for Part 4, subjects will have lipid panels performed at the screening visit, and fasting is not required.
[f] If screening serum pregnancy test was completed within 3 days before C1D1, a urine pregnancy test may be performed.
[redacted]

[redacted]

Table 25: Schedule of Timed Pharmacokinetic Assessments – Combination INCB057643 and Ruxolitinib (Part 3 C-ES-TGE and Part 4 C-EX-TGC)

Visit	Fasting Requirement	HOLD AM Dose	Predose[a]	Drug Administration	Time Postdose[a]					Drug Administration
					0.5 h ± 15 min	1 h ± 15 min	Snack or Meal	2 h ± 15 min	4 h ± 15 min	
C1D1	At least 8 h before the study drugs	N/A	X	Ruxolitinib	X	X	X	X	X	INCB057643
C1D8	At least 8 h before the study drugs	X	X	INCB057643	X	X	X	X	X	Ruxolitinib
C2D1	At least 8 h before the study drugs	X	X	INCB057643 + Ruxolitinib	X	X	X	X	X	N/A

[a] Collect timed PK samples predose (any time within 30 min of drug administration) and at 0.5 (± 5 min), 1 (± 15 min), 2 (± 15 min), and 4 (± 15 min) hours after drug administration on C1D1, C1D8 (+ 2 D), and C2D1 (± 2 D).

Table 26: Schedule of Assessments – Combination INCB057643 and Azacitidine (Part 3 C-ES-TGF and Part 4 C-EX-TGD)

Visit Day		Screening	Treatment					EOT	Safety Follow-Up
			28-Day Cycles (Anchored to Azacitidine Schedule)[a]						
		D-28 to D-1	D1	D8	D15	D22[b]	D29 to D42[c]		
Evaluation Window	**Section**		**± 2 D (C2D1+)**	**± 2 D**	**± 2 D**	**± 2 D**	**± 2 D**	**+ 3 D**	**30 to 35 D After EOT**
Informed consent	7.1	X							
Inclusion/exclusion criteria	3	X	X[d]						
Contact IRT	7.2	X	X					X	
Medical and cancer history	7.3	X							
Prior/concomitant medications	7.4	X[e]	X	X	X	X	X	X	X
Administer azacitidine in clinic[f]	5.2.2.6		X	X					
Administer INCB057643 in clinic	5.2.1.1		X	X	X				
Drug dispense/compliance check[g]	5.2.1.4, 5.3		X		X[h]		X[i]	X[h]	
Complete physical examination	7.5.2.1	X[j]						X	X
Targeted physical examination	7.5.2.2		X	X	X	X	X		
ECOG performance status	7.6.1	X	X					X	X
Vital signs/height/weight[k]	7.5.3	X[k]	X[k]	X	X	X	X	X[k]	X[k]
12-lead ECG	7.5.4.1	X	X					X	X
AE assessment	7.5	X	X	X	X	X	X	X	X
Laboratory assessments	0	X	X	X	X	X	X	X	X
Buccal swab	7.9.10	X							
AML disease assessment[l]	Appendix D	X	X					X	
Bone marrow examination[m]	7.7.4	X	X[l]						
Immunophenotyping[n]	7.7.5	X	When confirming response						
Provide reminder card	7.10.1	X	X	X	X	X	X	X	
Safety follow-up	6.4.1								X
Echocardiogram or MUGA	7.5.4.4		X					X	X

[a] From Cycle 4 onward, subjects are only required to receive azacitidine at the clinic on Day 1 of each cycle. All other azacitidine doses and study assessments may be performed at a local clinic. Day 8 assessments are not required beginning with Cycle 4. Data from local clinic assessments do not need to be entered into the eCRF.
[b] Day 22 assessments are performed in Cycle 1 only.
[c] If subjects have not sufficiently recovered from chemotherapy-related toxicities after 28 days, they will be seen weekly until such time that a subsequent cycle can be started. These visits will be entered as unscheduled visits in the eCRF. If subjects cannot start a subsequent cycles within 42 days, the site will contact the medical monitor.
[d] On C1D1 only, review inclusion/exclusion criteria before dose administration.
[e] Prior medications documented only at screening.
[f] Azacitidine will be administered as 75 mg/m^2 IV or SC for 7 days during a 9-day or less period (ie, a 2-day break allowed on weekend, if needed) of a 28-day cycle.
[g] All study drug for Cycle 1 will be dispensed at C1D1; subjects will bring unused study drug to the clinic for compliance check on C1D15. Study drug will be dispensed at Day 1 of all subsequent cycles, and compliance will be checked at the start of the next subsequent cycle.
[h] Compliance check only.

[i] If needed.
[j] Height measured at screening only.
[k] Weight required at screening, Day 1 of each cycle, EOT, and the safety follow-up visit.
[l] Investigators will perform disease and efficacy assessments per their own discretion. AML disease assessments will be performed on Day 1 of each cycle. Bone marrow biopsy and/or aspirates for response is to be performed at C4D1 or earlier, as clinically indicated, followed by every other month as clinically indicated, or upon circulating blood cell recovery, to assess anti-leukemic activity (cytogenetic testing is not required if CR is not present). Note: For subjects who have a significant blast count reduction (as determined by the investigator) but have not completely cleared circulating blasts, the C4D1 bone marrow is still strongly encouraged to be performed to assess the impact of treatment on the bone marrow blast content. See Section 7.7.4 for additional details.
[m] If a biopsy is not possible or contraindicated, or the tissue requirement cannot be satisfied, this requirement may be waived with approval from the medical monitor. Subjects with a history of allogenic hematopoietic stem cell transplantation will have tissue collected and analyzed locally for the purposes of determining disease status (where applicable), however, their sample does not need to be processed for sequencing due to chimeric potential.
[n] Immunophenotyping appropriate to AML will be conducted by flow cytometry at screening and when confirming CR.

Table 27: Schedule of Laboratory Assessments – Combination INCB057643 and Azacitidine (Part 3 C-ES-TGF and Part 4 C-EX-TGD)

Visit Day		Screening[a]	Treatment					EOT	Safety Follow-Up
			28-Day Cycles (Anchored to Azacitidine Schedule)						
		D-28 to D-1	D1	D8[b]	D15	D22	D29 to D42[c]		
Evaluation Window	**Section**		**± 2 D (C2D1+)**	**± 2 D**	**± 2 D**	**± 2 D**	**± 2 D**	**+ 3 D**	**30 to 35 D After EOT**
Overnight fast before visit[d]	7.8			X	X				
Serum chemistry	7.5.5.1	X	X[e]	X	X	X	X	X	X
Hematology with differential	7.5.5.1	X	X[e]	X	X	X	X	X	X
LFT panel	7.5.5.1	X	X[e]	X	X	X	X	X	X
Coagulation panel[f]	7.5.5.1	X	X[e]	X	X	X	X	X	X
Factor VII protein/antigen assay[f]	7.5.5.1	X	X[e]	X	X	X	X	X	X
Urinalysis[g]	7.5.5.1	X	X[g]					X	X[g]
Lipid panel[g]	7.5.5.1	X	X[g]					X	X
Hepatitis testing	7.5.5.3	X							
Serum pregnancy test	7.5.5.2	X[h]	X[h]					X	X
Cardiac troponin (either T or I)	7.5.5.4		X					X	X

[a] Screening laboratory tests must be performed within 14 days before C1D1.
[b] Day 8 assessments are not required beginning with Cycle 4. Day 22 assessments are performed in Cycle 1 only.
[c] If subjects have not sufficiently recovered from chemotherapy related toxicities after 28 days, they will be seen weekly until such time that a subsequent cycle can be started. These visits will be entered as unscheduled visits in the eCRF. If subjects cannot start a subsequent cycle within 42 days, the site will contact the medical monitor.
[d] Cycle 1 only.
[e] If completed within 3 days before C1D1, this laboratory assessment may be omitted.
[f] All subjects will have coagulation panel including Factor VII protein concentration by the Factor VII antigen assay conducted at screening, C1D1, C1D8, C1D15, C1D22, C2D1, C2D15, and C3D1. Coagulation panel is conducted on Day 1 of each subsequent cycle beginning with Cycle 4, more frequent if clinically indicated. Factor VII protein/antigen assay will also be collected upon a Grade 2 increased INR, or if clinically indicated. If the last Factor VII result before the EOT visit is within normal range, Factor VII does not need to be tested at EOT. If the Factor VII result at the EOT visit is within normal range, Factor VII does not need to be tested at the safety follow-up visit. If a subject is on a coumarin-based anticoagulant, such as warfarin, in addition to required testing per Protocol, coagulation panel may be tested as per standard of care or at the investigator's discretion. Study visits do not need to be delayed waiting on the Factor VII results as long as INR/PT results are eligible according to enrollment eligibility.
[g] Urinalysis and lipid panel only performed at Cycles 2, 4, and 7 and every 3 cycles there after (eg, Cycle 10, Cycle 13, etc) during the treatment period. If there are no clinically significant findings at EOT, urinalysis does not need to be performed at the safety follow-up visit.
[h] If screening serum pregnancy test was completed within 3 days before C1D1, a urine pregnancy test may be performed.

Table 28: Schedule of Timed Pharmacokinetic Assessments – Combination INCB057643 and Azacitidine (Part 3 C-ES-TGF and Part 4 C-EX-TGD)

Visit	Fasting Requirement	HOLD AM Dose	Predose[a]	INCB057643 Dose[b]	Azacitidine Dose	Time Postdose[a]					
						1 h ± 15 min	Snack or Meal	2 h ± 15 min	4 h ± 15 min	6 h ± 15 min	8 h ± 30 min
C1D8[c]	At least 8 h before the study drugs	N/A	X	♦	♦	X	X	X	X	X	X
C1D15	At least 8 h before the study drugs	X	X	♦		X	X	X	X	X	X

[a] Collect timed PK samples predose (any time within 30 minutes of INCB057643 administration) and at 1 (± 15 min), 2 (± 15 min), 4 (± 15 min), 6 (± 30 min), and 8 (± 30 min) hours after INCB057643 administration on C1D8 and C1D15.
[b] INCB057643 dose will be administered just before the daily dose of azacitidine.
[c] Use the ± 2-day window to ensure that the samples are collected on a day when both INCB057643 and azacitidine are administered.

Table 29: Schedule of Timed Translational/Pharmacodynamic Assessments – Combination INCB057643 and Azacitidine (Part 3 C-ES-TGF and Part 4 C-EX-TGD)

Sampling	Section	Treatment				EOT
		C1D1[a]	C2D1	C3D1	Bone Marrow Assessment[b]	
[redacted]						

Please refer to the Laboratory Manual for further instructions for collection.

[a] May be drawn after the subject signs the ICF, is approved for enrollment, and within 7 days before dose administration on C1D1.

[b] Investigators will perform efficacy assessments per their own discretion. Blood samplings will be conducted at each time when a bone marrow assessment is conducted for response.

[redacted]

Table 30: Local Laboratory Tests: Required Analytes

Blood Chemistries	Hematology	Serology[a]
Albumin ALP ALT AST Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose HbA1c[b] LDH Magnesium Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is > ULN)[c] Total protein Uric acid	CBC, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count Differential count, including[d]: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils • Blasts[e]	HBV surface antibody HBV surface antigen HBV core antibody HBV-DNA HCV antibody HCV-RNA
		Pregnancy
		Female subjects of childbearing potential require a serum pregnancy test at screening. Pregnancy tests (serum or urine) will be repeated during the study as required by local regulations.
		Coagulation
		PT aPTT INR Factor VII[f]
Lipids		**Urinalysis With Microscopic Examination**
Total cholesterol Triglycerides LDL HDL		Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen
mCRPC Only		
PSA		
Cardiac Monitoring		
Cardiac troponin (either T or I)		

[a] Hepatitis B and C viral loads by PCR assay only need to be assessed when respective serology results are positive. Hepatitis B virus DNA does not need to be performed if the surface antibody is the only positive result.
[b] HbA1c needs to be performed for every subject during screening for eligibility and when clinically indicated during the study.
[c] Direct bilirubin will only be performed when total bilirubin is > ULN and the subject does not have Gilbert's syndrome.
[d] Absolute values must be provided for lymphocytes and neutrophils.
[e] Required at intervals specified where peripheral blast count is part of disease assessments such as AML or HR-MDS, MDS/MPN and MF.
[f] All subjects will have coagulation panel and factor VII conducted as indicted in the laboratory schedule of assessments.

6.1. Screening

Screening is the interval between signing the ICF and the day the subject is enrolled in the study (Cycle 1 Day 1). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the subject's routine clinical management (eg, blood count, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been

performed in the timeframe of the study (ie, within 28 days of Cycle 1 Day 1). All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before initiation of study treatment will be used to determine subject eligibility. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status (eg, after recovery from an infection).

6.2. Treatment

6.2.1. Day 1

The treatment period begins on the day the subject receives the first dose of study drug; in Parts 1 and 2 this is defined as Cycle 1 Day 1 and continues until a decision is made to permanently discontinue the study drug. In Parts 3 and 4, Cycle 1 Day 1 is defined as the first day of SOC agent administration. At Cycle 1 Day 1, results from screening assessments will be reviewed to determine if the subject continues to meet the eligibility requirements as specified in the Protocol.

6.2.2. Visit Scheduling

Dates for subsequent study visits will be determined based on Cycle 1 Day 1, and should occur within the allowable visit window of the scheduled date unless delayed for safety reasons. For combination therapy groups, Day 1 of each study cycle will correspond with the first day of SOC agent administration in that cycle; thus study cycles may become out of sync with the originally planned disease assessment schedule. **In this event, disease assessments will remain on the original schedule for that treatment group and will be measured from the baseline (screening) disease assessment.** All other assessments will shift to coincide with the revised treatment (cycle) schedule. For example, if one of the SOC agents has a delay in beginning therapy on Cycle 2 Day 1, the next scheduled visit when SOC agent is administered will be Cycle 2 Day 1 and all other assessments will coincide with that Cycle 2 Day 1 visit schedule. All planned assessments are shown in Section 6. Other clinical assessments, or PK/PD assessments, may be added if medically indicated or indicated by emerging data, to maintain safety.

6.3. End of Treatment

If a decision is made that the subject will permanently discontinue study drug, the EOT visit will be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will be conducted in addition to those required for the regularly scheduled visit, and the data will be entered in the EOT visit in the eCRF. The subject should be encouraged to return for the safety follow-up visit.

6.4. Follow-Up

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and 30 days after the last dose of study drug or the scheduled follow-up visit, whichever is later. Reasonable efforts should be made to have the subject return for the safety follow-up visit, to be scheduled 30 to 35 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed) and to report any AEs that occur during this time. Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

6.4.2. Unscheduled Visits

Clinic visits or diagnostic laboratory visits not prescribed in the Protocol may be performed at any time clinically indicated. Results of assessments performed at these visits will be entered as "unscheduled" visits in the eCRF. The sponsor may also request additional visits to be performed, if needed, based on emerging safety data.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

All study assessments and procedures detailed in this section are to be performed as indicated in the appropriate schedule of assessments (see Section 6).

7.1. Administration of Informed Consent Form

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

7.2. Interactive Response Technology Procedure

The investigator or designee will assign a subject ID number when a subject enters the screening phase. The IRT will be contacted at each visit at which study drug is dispensed to update the study drug supply. Refer to the IRT manual for detailed instructions. Additional details regarding the IRT may be referenced in Section 5.1.1.

7.3. Demography and Medical History

Demographic data and a complete medical and medication history will be collected at screening. This will include date of birth, race, ethnicity, and medical and surgical history for the disease under study. Details regarding the disease for which the subject has enrolled in this study (eg, date of diagnosis, primary tumor histology, prior systemic therapies, surgeries, radiation therapy, and stage of cancer) will be recorded separately and not listed in medical history.

7.3.1. Transfusion History Status (Myelofibrosis Combination Cohorts Only)

All transfusions of red blood cell products or platelets from at least 16 weeks before the screening visit will be recorded. The product(s) delivered, date of transfusion, and units delivered will be recorded in the eCRF.

7.3.2. Screening Symptom Form (Myelofibrosis Combination Cohorts Only)

In order to satisfy inclusion criteria for Part 3 C-ES-TGE and Part 4 C-EX-TGC, active symptoms of MF at screening, as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form, will be recorded in the eCRF (see Appendix P).

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. Prior medications will be documented at screening only. All concomitant medications and measures must be recorded in the eCRF, and any medication received or procedures performed within 30 days before the first dose and through the safety follow-up period will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

7.5. Safety Assessments

7.5.1. Adverse Events

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

7.5.2. Physical Examinations

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

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

7.5.2.1. Comprehensive Physical Examination

The comprehensive physical examination will include height (at screening only), body weight, and assessment of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; lymph nodes; and a brief neurological examination. Disease-specific features (eg, plasmacytomas in MM subjects) that can be appreciated on physical examination will be noted as well.

7.5.2.2. Targeted Physical Examination

The targeted physical examination will be a symptom-directed evaluation. The targeted physical assessment will evaluate the body systems or organs, as indicated by subject symptoms, AEs, or other findings.

7.5.3. Vital Signs and Weight

Vital sign measurements include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the subject in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs. On Day 1 of each cycle, weight will be assessed for all subjects.

7.5.4. Cardiac Monitoring

7.5.4.1. Twelve-Lead Electrocardiograms

The sites will use their own local ECG machine to obtain ECGs per the schedule of assessment tables. The 12-lead ECGs will be interpreted by the investigator at the site for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Any treatment-emergent ECG finding occurring on study that is abnormal and clinically significant in the judgment of the investigator will be reported as an AE.

7.5.4.2. Electrocardiogram Procedures

All 12-lead ECGs will be performed with the subject in a recumbent position after 5 minutes of rest and will not be performed within 15 minutes after a blood collection. A single 12-lead ECG will be performed at each timepoint indicated in the appropriate schedule of assessments; when timed ECGs are required, the additional procedures are outlined in Section 7.5.4.3.

7.5.4.3. Additional Instructions for Timed Electrocardiograms (Part 1 and Part 2 Only)

Timed triplicates ECGs will be conducted before the clinic administration of study drug (predose) and using the timed schedule shown in Table 9.

All timed ECGs conducted will be performed in triplicate. The ECGs will be conducted before, but within 15 minutes of, the PK blood collection at the corresponding timepoint. The specified postdose timepoints may be adjusted based on emerging PK data.

7.5.4.4. Echocardiogram or MUGA

Echocardiogram or MUGA, as per investigator discretion, will be performed according to institution guideline on Day 1 of each cycle, EOT, and 30-day safety follow-up. The same methodology should be used for each subject. Ejection fraction will be calculated from each echocardiogram or MUGA assessment according to established guideline.

7.5.5. Laboratory Assessments

7.5.5.1. Chemistry, Hematology, Urinalysis, Coagulation Panel, Factor VII, Serology, and Endocrine Function Testing

Chemistry, hematology, coagulation panel, Factor VII, serology, and endocrine function will all be analyzed by the local site laboratory. The investigative site will not enter the local laboratory results and laboratory normal ranges into the eCRF unless the abnormal laboratory values are considered reportable as clinically significant AEs, in which case they should be entered into the eCRF as an AE. All local laboratory assessments will be performed using standard procedures on the days indicated in the appropriate schedule of assessments. Table 30 lists the required laboratory tests in each category; additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

On Day 1, laboratory data must be reviewed to confirm eligibility to start treatment (both monotherapy and combination therapy). Laboratory samples collected for the Day 1 evaluation must be performed before dose administration on Day 1. After Cycle 1, predose laboratory procedures can be conducted within the allowed visit window, and results will be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

7.5.5.2. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential before first dose of study drug (as applicable). Subsequently, pregnancy tests (either serum or urine, unless otherwise indicated) may be conducted as medically indicated or as required per local guidelines. If the screening serum pregnancy test is completed within 3 days before Cycle 1 Day 1, a urine pregnancy test may be performed on Cycle 1 Day 1.

7.5.5.3. Hepatitis Screening Tests

Testing for hepatitis (detailed in Table 30) is required at screening, and results will be reviewed before Day 1 to confirm eligibility. Generally hepatitis serology tests should be submitted early in the screening process because of the length of time frequently needed to obtain the results. If hepatitis B and/or C serology results are positive, subjects will be required to undergo additional testing for HBV-DNA and HCV-RNA by polymerase chain reaction (PCR) assay to assess active infection. Subjects with chronic (carrier state) or cleared hepatitis B or C will be allowed to enroll. For hepatitis B, chronic disease (carrier state) is defined as subjects with positive HBV surface antigen and positive HBV total core antibody but with negative HBV core antibody immunoglobulin M (IgM) and positive HBV antibody; these subjects would have low risk of liver damage.

7.5.5.4. Cardiac Troponin (Either T or I) Testing

Cardiac troponin (T and/or I) test will be performed according to institutional guideline on Day 1 of each cycle, EOT, and 30-day safety follow-up.

7.6. Performance and Health-Related Quality of Life Assessments

7.6.1. ECOG Performance Status

An ECOG performance score will be required at screening to evaluate eligibility and will be assessed at other study visits noted in the appropriate schedule of assessments. Performance status must be assessed by a medically qualified individual and recorded in the eCRF.

7.7. Efficacy Assessments

The following disease response criteria will be used for each of the malignancies included in this study:

- AML: International Working Group Response Criteria for Acute Myeloid Leukemia (Cheson et al 2003; Appendix D)
  - Additionally, peripheral blood blast response will be used, which is defined as clearance of AML blasts in the peripheral blood lasting more than 4 weeks.
- Glioblastoma Multiforme: Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology (RANO) Working Group (Wen et al 2010; Appendix E)
- MDS: International Working Group Response Criteria For Myelodysplastic Syndrome (Cheson et al 2006; Appendix F)
- MDS/MPNs: International Consortium Proposal of Uniform Response Criteria for Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) In Adults (Savona et al 2015; Appendix G)
- MF: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report (Tefferi et al 2013; Appendix H):
  - Spleen response will be used as the preliminary efficacy endpoint for MF subjects.
- MM: International Uniform Response Criteria for Multiple Myeloma (Durie et al 2006; Appendix I)
- MM (minimal response only): Criteria for Evaluating Disease Response and Progression in Patients With Multiple Myeloma Treated by High-Dose Therapy And Haemopoietic Stem Cell Transplantation: Myeloma Subcommittee of the European Society for Blood and Marrow Transplantation (EBMT; Blade et al 1998; Appendix J)
- Lymphoma: Response Criteria For Lymphoma – The Lugano Classification (Cheson et al 2014; Appendix K)

- Solid tumors: RECIST v1.1 (Eisenhauer et al 2009):
  - Objective response rate will be used as the preliminary efficacy endpoint for any measurable disease according to RECIST v1.1.
- Waldenström macroglobulinemia: VIth International Workshop on Waldenström macroglobulinemia response assessment for subjects with Waldenström macroglobulinemia (Owen et al 2013; Appendix L)
- Chronic lymphocytic leukemia (CLL): International Workshop on Chronic Lymphocytic Leukemia criteria for CLL (Hallek et al 2008, Cheson et al 2012; Appendix M)
- Prostate Cancer Clinical Trial Working Group 3 (Sher et al 2016; Appendix N):
  - Prostate-specific antigen response and ORR will be used as the preliminary efficacy endpoints for mCRPC subjects.

Efficacy assessments will be performed at screening (this will be considered the baseline disease assessments) and at the intervals according to local standards or at the investigator's discretion.

7.7.1. Lymphoma, Chronic Lymphocytic Leukemia, and Myelofibrosis: CT Scan or MRI

If CT or MRI is used as a functional imaging tool for staging or response assessment of lymphoma as a part of the standard of care (based on the specific histotype of that subject) or MF, the results obtained during any study phase will be captured in the eCRF. If CT or MRI assessment was performed, under standard of care, before the signing of the ICF but within 30 days of Cycle 1 Day 1, the result of that assessment may be recorded in the eCRF in lieu of a study-specific assessment. The same imaging modality will be used throughout the study in evaluating response.

7.7.1.1. MRI or CT Scan in Myelofibrosis Combination Cohort Subjects

For MF combination cohort subjects only, the primary measure of spleen size will be by MRI (or CT scan in applicable subjects). An MRI of the upper and lower abdomen and pelvis will be performed at baseline and every 12 weeks thereafter through Week 108. An MRI will be performed with a body coil, because the objective is to measure organ volume, not to find very small lesions. The MRIs will be read by local radiologists, and all images for a subject (baseline and on-treatment scans) must be read by the same reader. Spleen and liver volume will be obtained by outlining the circumference of the organ and determining the volume using the validated technique of least squares. The MRI will not determine spleen length below the costal margin, as there are no validated approaches for determining this measurement.

An MRI is the preferred method for obtaining spleen volume data. However, CT scans may be performed at the visits where MRI is designated if the subject is not a candidate for MRI (eg, because of the presence of metal clips in the body, because of claustrophobia) or if MRI is not readily available. Note: the same method (MRI vs CT) must be used for all visits for a given subject unless a new contraindication to the use of MRI occurs (eg, pacemaker insertion).

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

If [^{18}F] fluorodeoxyglucose (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 (based on the specific histotype of that subject), the results obtained during any study phase will be captured in the eCRF. If PET or PET/CT assessment was performed, under standard of care, before signing of the ICF but within 30 days of Cycle 1 Day 1, the result of that assessment may be recorded in the eCRF in lieu of a study-specific assessment. The same imaging modality will be used throughout the study in evaluating response.

7.7.3. Solid Tumors and Lymphoma: Tumor Biopsy

Baseline tumor biopsy samples are required for subject participation in all parts of the study, except for subjects with glioblastoma. Fresh biopsies are preferred, however a biopsy of research quality obtained for other purposes may be used if the subject has not had any intervening systemic therapy from the time of the biopsy to the start of treatment (Cycle 1 Day 1) and if 25 slides or tissue block may be submitted. See Section 7.9.9 for additional details. In addition to baseline tumor biopsy samples, biopsy during treatment and/or at disease progression is strongly recommended but not mandatory. Subjects who obtain a biopsy while on treatment, or at disease progression will need to sign an additional ICF for "optional tumor biopsy while on treatment." The consent for on-treatment biopsy can be withdrawn by the subject at any time during the study. If the subject signs the ICF for on-treatment biopsy, the feasibility of the on-treatment biopsy will be evaluated by the investigator and/or radiologist at the time of the biopsy.

7.7.4. Leukemia, High-Risk Myelodysplastic Syndrome, Myelodysplastic Syndrome/Myeloproliferative Neoplasm, Myelofibrosis, and Multiple Myeloma: Bone Marrow Biopsy

Bone marrow examination (aspirate and biopsy) is required at screening for subjects with diseases that are typically monitored though bone marrow examination, including leukemia, HR-MDS, MM, MDS/MPN, and MF. If disease status requires assessment with bone marrow aspirate or biopsy, subjects with leukemia, HR-MDS, MDS/MPN, or MF will have a bone marrow aspirate and/or 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. If possible, bone marrow examinations should be scheduled to coincide with other disease assessments, including peripheral blood or, for MF, imaging studies.

For AML subjects, bone marrow disease assessment during Cycle 2 is strongly recommended unless contraindicated.

Subjects with MM only require a postbaseline bone marrow examination to confirm CR, after 2 consecutive laboratory disease assessments (Durie et al 2006) demonstrating negative serum and/or urine immunofixation, and as clinically indicated.

Data from the pathology report result from the bone marrow examination will be captured in the eCRF. All bone marrow examinations will include a unilateral aspiration and biopsy with fluorescence *in situ* hybridization (FISH) and cytogenetic testing, when feasible. Subjects may be enrolled based on a biopsy only when a "packed marrow" precludes aspiration at the discretion of the medical monitor. Results of assessments performed under standard of care

before the signing of ICF may be used as the baseline disease assessment in lieu of a study-specific procedure if performed within 60 days of the first dose of study drug (Cycle 1 Day 1).

7.7.5. Leukemia and Lymphoma: Immunophenotyping

For subjects with leukemia, lymphoma, MDS/MPN, and MF, immunophenotyping appropriate to the underlying pathology will be conducted by flow cytometry at the local laboratory at screening and at subsequent times only as part of confirmation of response. If appropriate to the histologic subtype, immunophenotyping will be performed at screening and may be conducted on study in subjects with lymphoma as part of routine standard of care and/or at response assessment. Results will be captured in the eCRF.

7.7.6. Leukemia, HR-MDS, and MDS/MPN: Peripheral Blood Blast Counts

For disease assessment timepoints in leukemia, HR-MDS, and MDS/MPN, peripheral blood blast counts (appropriate to underlying pathology) will be evaluated by microscopic evaluation or other appropriate methodology and will be used as appropriate in conjunction with other parameters (eg, complete blood counts [CBCs]) in determining disease status.

7.7.7. Multiple Myeloma: Disease Assessment

Multiple myeloma laboratory assessments will be performed as per the schedule in Table 9 (as applicable). Required analytes for MM disease assessments are detailed in Table 31. In addition, a bone marrow examination (aspirate and biopsy) will be required to confirm CR.

Table 31: Required Analytes for Multiple Myeloma Subjects

Routine Disease Assessment
• Serum protein electrophoresis with quantitative M-protein • Urine protein electrophoresis with quantitative M-protein • Quantitative immunoglobulins • Serum FLCs • Beta-2 microglobulin
Baseline, Confirming CR and as Clinically Indicated
• Bone marrow aspirate and biopsy • FISH/cytogenetics

Note: For subjects who do not show evidence of urine paraprotein at screening, only spot urine with urine protein electrophoresis required; if the subject subsequently shows evidence of urine paraprotein, a 24-hour collection will be required along with the urine protein electrophoresis.

7.7.8. Multiple Myeloma: Skeletal Survey

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

7.7.9. Myelofibrosis: Spleen Palpitation (Myelofibrosis Combination Cohorts Only)

Spleen length will be assessed by manual palpation at every study visit (laboratory-only visits not included) and will be used for routine subject management. Investigators will be provided with a soft centimeter ruler so that palpable spleen length is measured in centimeters instead of in

finger breadths. The edge of the spleen shall be determined by palpation and measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion. Spleen length must be recorded in the eCRF.

7.7.10. Castrate Resistant Prostate Cancer: Prostate Cancer Clinical Trials Work Group 3

The disease assessments of mCRPC subjects will be conducted as defined by the PCWG3 guidelines (see Appendix N) as indicated in Table 20 and Table 21, including ECOG every cycle, laboratory parameters (ie, PSA, ALP, lactate dehydrogenase [LDH], serum chemistry, and CBC) every cycle, and imaging (bone scans and CT/MRI) every 8 to 9 weeks for the first 24 weeks and then every 12 weeks thereafter. Patient outcomes/analgesic consumption tools will not be used in this study.

7.8. Pharmacokinetic Assessments

7.8.1. Blood Sample Collection

Pharmacokinetic samples will be obtained to evaluate plasma PK parameters as described in Appendix B. The study drug will be administered in clinic with approximately 240 mL of water. Subjects will remain fasting from food for 8 hours predose and at least 1 hour postdose, after which a meal or snack may be consumed. For PK sample collection, the following will be recorded:

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

Subjects will receive reminder cards in advance of the study visit providing instructions to prepare for the visit (see Section 7.10.1). Instructions for plasma preparation and sample shipping will be provided in the Laboratory Manual. The specified postdose timepoints may be adjusted based on emerging PK data.

7.8.2. Urine Sample Collection

A predose void must be collected and the time recorded. Urine will be collected from all subjects at Cycle 1 Day 8 after administration of INCB057643 and a predose void. Total urine will be collected over an 8-hour interval following study drug administration. Urine containers will be kept at reduced temperature (refrigerated or ice bath) during collection. After the interval, the total urine volume and the pH will be measured and recorded in the individual eCRF. Urine will be mixed thoroughly, and two 10 mL aliquots will be collected into a prelabeled, polypropylene storage bottle and frozen at or below -20°C. Shipping and handling instructions will be provided in the Laboratory Manual; samples will be analyzed by the sponsor or the sponsor's designee for parameters described in Appendix B.

7.8.3. Bioanalytical Methodology and Analysis

Plasma samples will be analyzed by the sponsor or the sponsor's designee using a validated assay. [redacted] Pharmacokinetic parameters that will be analyzed are shown in Appendix B, and the analysis methodology is described in Section 9.4.3.

7.8.4. Food-Effect Pharmacokinetic Testing

Pharmacokinetic testing for food effect on drug exposure will be performed in the first 12 subjects enrolled into Part 2/TGA only. Additional subjects may be enrolled if there are data quality issues among the initial 12 subjects. There will be no food-effect PK testing conducted in Part 3 or Part 4. Subjects may be excused from the food-effect portion of the study if they are unable to consume the meal.

Subjects 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 study drug. Subjects must consume the entire breakfast within 25 minutes, and study drug administration will begin 5 minutes after completing breakfast.

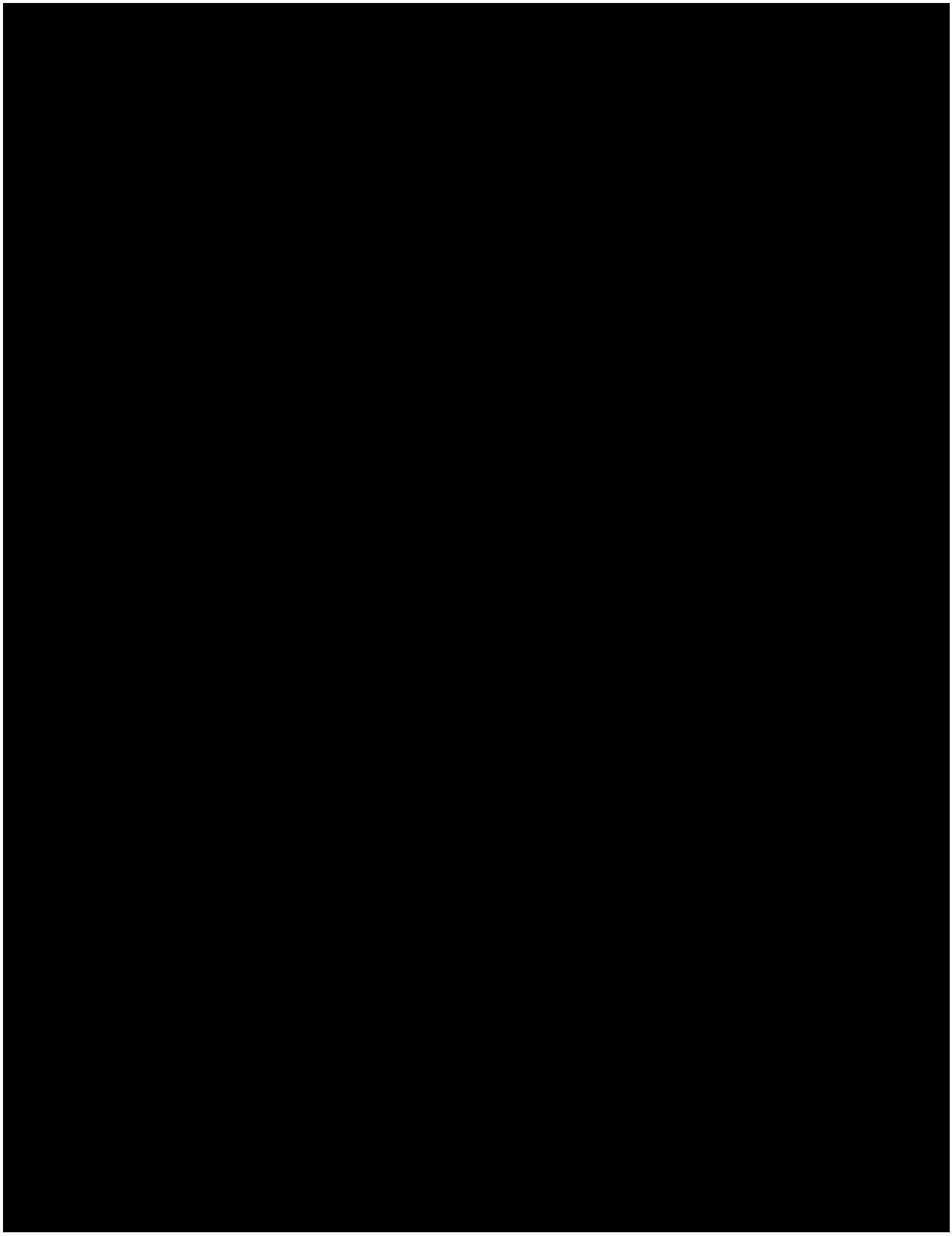
The high-fat, high-calorie breakfast (50% kcal from fat) will consist of:

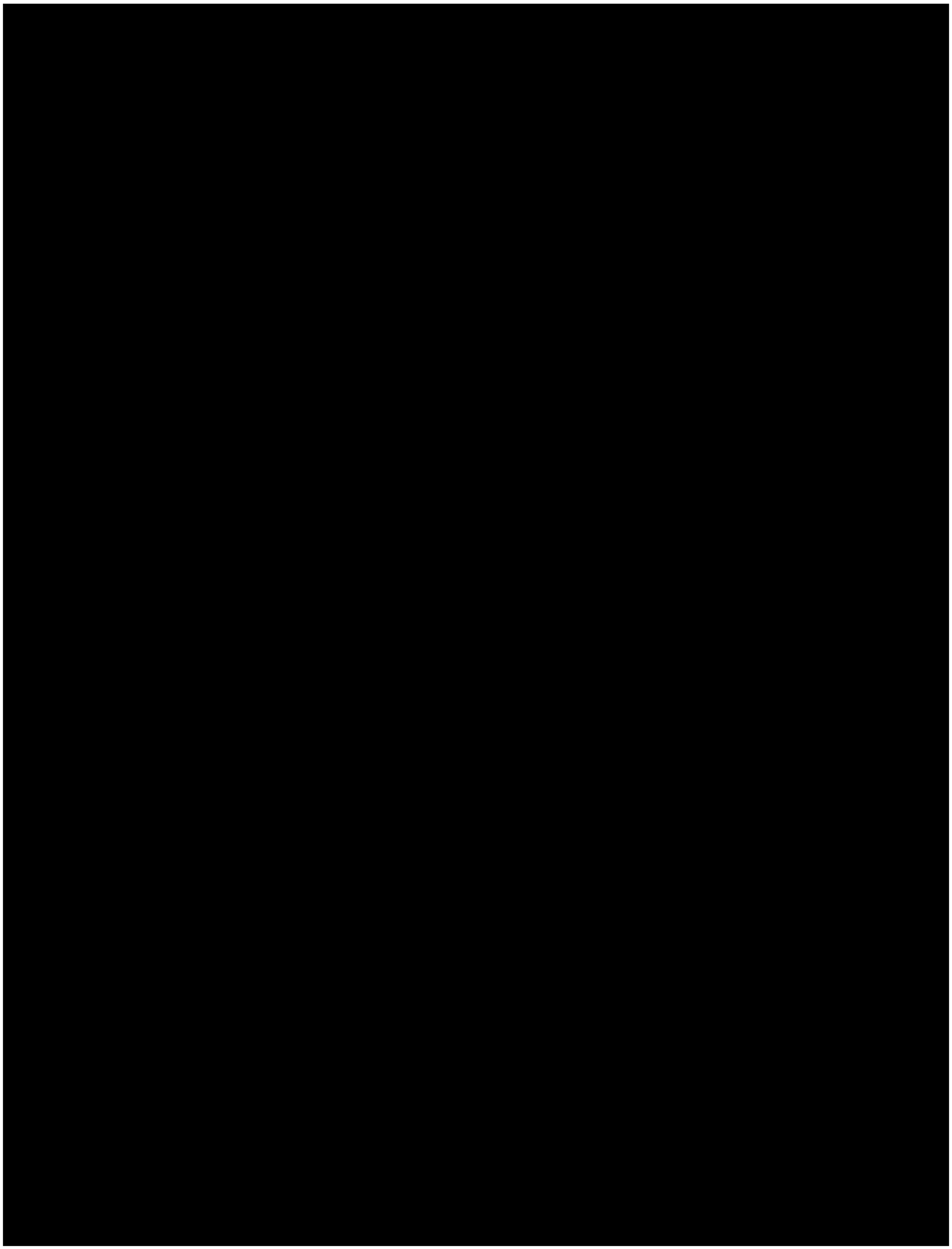
- 2 eggs fried in butter
- 2 strips of bacon
- 1 English muffin with butter
- 4 oz hash brown potatoes
- 8 oz whole milk

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

Pharmacokinetic samples for food-effect are collected only on the first 12 subjects in Part 2/TGA, only in Cycle 2, as follows: at predose (after the meal and before study drug administration) and at 0.5 (± 5 min), 1 (± 15 min), 2 (± 15 min), 4 (± 15 min), 6 (± 30 min), and 8 (± 30 min) hours after administration on Cycle 2 Day 1 and predose Cycle 2 Day 2.

[redacted]





[redacted]

7.10. Other Study Procedures

7.10.1. 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 before visits on which PK draws will be performed. Reminder cards will also include instructions specific for study visits at which the study drug will be administered in clinic. All necessary instructions, such as those for study drug administration, concomitant medications, and laboratory tests will be provided to the subject in writing on this reminder card or on accompanying written materials.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

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

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 30 days after the last dose of study drug. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

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

reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the Adverse Events form of the eCRF.

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

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

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

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

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

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

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

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

8.2. Laboratory Test Abnormalities

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

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

8.3. Serious Adverse Events

8.3.1. Definitions

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

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

- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 30 days after the last dose of study drug, whichever is later) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Any SAEs occurring more than 30 days after the last dose of study drug should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study drug.

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

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

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

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

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

relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

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

- The study drug must be discontinued immediately (female subjects only; see Section 5.4.2 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

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

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

8.6. Warnings and Precautions

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

8.7. Data Monitoring Committee

Not applicable.

8.8. Product Complaints

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

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

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

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

9. STATISTICS

9.1. Study Populations

The populations to be analyzed include the following:

- The safety evaluable population includes all subjects who are enrolled and received at least 1 dose of study drug. This population will be used in the analyses of safety, study drug administration, and compliance data.
- The efficacy evaluable population includes all subjects who are enrolled and received at least 1 dose of study drug. This population will be used in the analyses of demographic, baseline, and efficacy data.
- The PK evaluable population includes all subjects who received at least 1 dose of study drug and had at least 1 PK sample collected and analyzed.
- The PD evaluable population includes all subjects who received at least 1 dose of study drug and had at least 1 PD sample collected and analyzed.

9.2. Selection of Sample Size

Part 1 is a standard dose-escalation design, and the sample size depends on the occurrence of safety finding such as DLTs. Approximately 3 to 6 subjects will be enrolled in each dose level. Using this design, the probability of dose escalation for various DLT rates is given in Table 32.

Table 32: Probability of Dose Escalation by DLT Rate

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

Part 2/TGA will enroll up to approximately 165 subjects with specified solid tumors or lymphoma. Approximately 5 to 15 subjects will be enrolled in the pancreatic adenocarcinoma, breast cancer, glioblastoma multiforme, Ewing's sarcoma, and NHL groups. The high-grade

serous ovarian cancer and mCRPC groups will include approximately 20 subjects each. The tumor group of any solid tumor or lymphoma (except the specified) with any pathway alteration relevant to BET protein signaling, such as MYC pathway activation, will enroll up to 20 subjects as well.

Part 2/TGB will enroll up to 45 subjects with AML, HR-MDS, MDS/MPN, or MF; and Part 2/TGC will enroll up to 15 subjects with MM. This will provide > 80% chance of detecting at least 1 responder if the underlying response rate is 30%.

Part 3 will use a 3 + 3 design to evaluate different doses of INCB057643 in combination with gemcitabine, paclitaxel, rucaparib, abiraterone, ruxolitinib, or azacitidine in 6 treatment groups. Dose escalation for 6 treatment groups will proceed independently. Approximately 3 to 6 subjects will be enrolled in each dose level for each treatment group. The total number of subjects will depend on the frequency of DLTs and the number of dose levels tested before the MTD and RP2D are reached. Using this design, the probability of dose escalation for various DLT rates is given in Table 32.

In Part 4, approximately 71 subjects will be enrolled across 4 possible expansion treatment groups to further evaluate the safety, tolerability, efficacy, PK, and PD of the RP2Ds selected from Part 3. Cohorts for ovarian and mCRPC will enroll up to 20 subjects each. The MF cohort will enroll approximately 16 subjects, and the AML/HR-MDS cohort will enroll 15 subjects. This will provide > 80% chance of detecting at least 1 responder if the underlying response rate is 30%.

9.3. Level of Significance

No formal statistical tests will be performed. All CIs will be reported with 95% confidence level.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

There is no primary efficacy analyses due to the nature of the study.

9.4.1.2. Secondary Efficacy Analyses

- Objective response rate is defined as the proportion of subjects who have an objective response using the applicable disease assessment criteria. Objective response rate will be estimated with 95% CI, which will be calculated based on the exact method for binomial distributions.

[redacted]

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

A treatment-emergent AE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to treatment-emergent AEs, but data listings will include all AEs regardless of their timing relative to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the NCI CTCAE v4.03 using Grades 1 through 4.

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

9.4.2.2. Clinical Laboratory Tests

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

Laboratory data will be classified into Grades 1 through 4 using CTCAE v4.03. The following summaries will be produced for the laboratory data:

- Number and percentage of subjects with worst postbaseline CTCAE grade (regardless of baseline value). Each subject will be counted only for the worst grade observed postbaseline.
- Shift tables from baseline to the worst postbaseline value using CTCAE grade.
- For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges.

9.4.2.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 33), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 33: Criteria for Clinically Notable Vital Sign Abnormalities

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

9.4.2.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (Table 34). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 34: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 460 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
RR	> 1330 ms	< 600 ms

QTcF = Fridericia correction.

9.4.3. Pharmacokinetic Analysis

The PK parameters of C_{max}, T_{max}, C_{min} (INCB057643), $AUC_{0\text{-}t}$, $AUC_{0\text{-}\tau}$ (INCB057643) and Cl/F (INCB057643) will be calculated from the blood plasma concentrations of INCB057643 using standard noncompartmental (model-independent) PK methods. Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin® (Pharsight Corporation, Mountain View, CA). Nominal times will be used in all cases, except when the difference between the actual time and nominal time is > 15 minutes for samples collected up to 4 hours after administration and > 30 minutes for samples collected more than 4 hours after administration; in these cases, actual time will be used for PK analysis. The PK parameters of INCB057643 will be summarized by descriptive statistics by part, treatment, and dose group. For the food-effect portion of the study, the log-transformed PK parameters will be compared between the fed and fasted treatments using an analysis of variance for a 1-way crossover design. The geometric mean relative bioavailability and 90% CIs will be calculated for comparing C_{max} and AUC between the fed (test) and fasted (reference) treatments. Additional details of analyses will be described in the Statistical Analysis Plan.

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

9.4.4. Pharmacodynamic Analysis

Tumor biopsy samples will be used by the sponsor or its designee to investigate molecular signatures associated with response or resistance to treatment with the study drug. DNA and/or RNA may be extracted from these samples to perform somatic mutation analysis and genetic expression analysis, including that of known oncogenes. Chromosomal alterations may be examined. [redacted]

Somatic mutations in tumor samples may be confirmed by assessing the specific sequence change in a normal sample obtained by buccal swab or peripheral blood from the whole blood PD sample.

Plasma analytes may include cytokines and other markers of inflammation and immune status, tumor markers, and markers of metabolism and nutritional status. [redacted]

Correlative PD analysis will utilize markers available in whole blood to identify associations with response or safety and may include examining plasma or serum for circulating free DNA or RNA or examining specific cell populations using standard methods. Such analyses may be conducted by the sponsor or designee.

Data will be analyzed and presented using summary statistics.

9.5. Analyses for the Data Monitoring Committee

Not applicable.

9.6. Interim Analysis

No interim analysis is planned.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

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

The investigator will be responsible for:

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all subjects.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other

study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

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

10.2. Accountability, Handling, and Disposal of Study Drug

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

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

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

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

10.3. Data Management

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

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

Protocol deviations will be identified and recorded in the Protocol Deviation form of the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified

is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

10.4. Data Privacy and Confidentiality of Study Records

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

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

10.5. Financial Disclosure

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

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

10.6. Publication Policy

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

11. REFERENCES

Abraxane (paclitaxel) [summary of product characteristics]. Uxbridge, United Kingdom: Celgene Europe Limited; 2016.

Al-Ali HK, Jaekel N, Junghanss C, et al. Azacitidine in patients with acute myeloid leukemia medically unfit for or resistant to chemotherapy: a multicenter phase I/II study. Leuk Lymphoma 2012;53:110-117.

Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014;371:1028-1038.

Asangani IA, Dommeti VL, Wang X, et al. Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer. Nature 2014;510:278-282.

Auchus RJ, Yu MK, Nguyen S, Mundle SD. Use of prednisone with abiraterone acetate in metastatic castration-resistant prostate cancer. Oncologist 2014;19:1231-1240.

Belkina AC, Nikolajczyk BS, Denis GV. BET protein function is required for inflammation: BRD2 genetic disruption and BET inhibitor JQ1 impair mouse macrophage inflammatory responses. J Immunol 2013;190:3670-3678.

Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation: Myeloma Subcommittee of the EBMT, European Group for Blood and Marrow Transplant. Br J Haematol 1998;102:1115-1123.

Bubley GJ, Balk SP. Association between androgen receptor splice variants and prostate cancer resistance to abiraterone and enzalutamide. J Clin Oncol 2017;35:2103-2105.

Ceresoli GL, Gregorc V, Cordio S, et al. Phase II study of weekly paclitaxel as second-line therapy in patients with advanced non-small cell lung cancer. Lung Cancer 2004;44:231-239.

Ceribelli M, Kelly PN, Shaffer AL, et al. Blockade of oncogenic IκB kinase activity in diffuse large B-cell lymphoma by bromodomain and extraterminal domain protein inhibitors. Proc Natl Acad Sci U S A 2014;111:11365-11370.

Cervantes F, Vannucchi AM, Kiladjian JJ, et al. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. Blood 2013;122:4047-4053.

Chandrasekar T, Yang JC, Gao AC, Evans CP. Mechanisms of resistance in castration-resistant prostate cancer (CRPC). Transl Androl Urol 2015;4:365-380.

Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003;21:4642-4649.

Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol 2012;30:2820-2822.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;20:3059-3068.

Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-425.

Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 15, 2014. http://www.hma.eu/ctfg.html. Accessed December 15, 2015.

Dawson MA, Prinjha RK, Dittmann A, et al. Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. Nature 2011;478:529-533.

Delmore JE, Issa GC, Lemieux ME, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell 2011;146:904-917.

Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with > 30% blasts. Blood 2015;126:291-299.

Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-1473.

Efstathiou E, Titus M, Tsavachidou D, et al. Effects of abiraterone acetate on androgen signaling in castrate-resistant prostate cancer in bone. J Clin Oncol 2012;30:637-643.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247.

Elit L, Hirte H. Palliative systemic therapy for women with recurrent epithelial ovarian cancer: current options. Onco Targets Ther 2013;6:107-118.

Emanuel RM, Dueck AC, Greyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol 2012;30:4098-4108.

Filippakopoulos P, Knapp S. Targeting bromodomains: epigenetic readers of lysine acetylation. Nat Rev Drug Discov 2014;13:337-356.

Filippakopoulos P, Qi J, Picaud S, et al. Selective inhibition of BET bromodomains. Nature 2010;468:1067-1073.

Food and Drug Administration (FDA). Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2009. http://www.fda.gov/downloads/Drugs/Guidances/UCM174090.pdf. Accessed September 25, 2017.

French CA, Ramirez CL, Kolmakova J, et al. BRD-NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells. Oncogene 2008;27:2237-2242.

Gemzar (gemcitabine) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; 2017.

Gemzar (gemcitabine) [summary of product characteristics]. Indianapolis, IN: Eli Lilly and Company; 2008.

Giacinti S, Bassanelli M, Aschelter AM, Milano A, Roberto M, Marchetti P. Resistance to abiraterone in castration-resistant prostate cancer: a review of the literature. Anticancer Res 2014;34:6265-6269.

Grabosch SM, Edwards RP, Helm CW. Ovarian cancer treatment protocols. Medscape 2017. http://emedicine.medscape.com/article/2006723-overview. Updated April 3, 2017. Accessed September 28, 2017.

Gynecologic Oncology Group, Markman M, Blessing J, et al. Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. Gynecol Oncol 2006;101:436-440.

Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-5456.

Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med 2012;366:787-798.

Hensel T, Giorgi C, Schmidt O, et al. Targeting the EWS-ETS transcriptional program by BET bromodomain inhibition in Ewing sarcoma. Oncotarget 2016;7:1451-1463.

Huang B, Yang XD, Zhou MM, Ozato K, Chen LF. BRD4 coactivates transcriptional activation of NF-kappaB via specific binding to acetylated RelA. Mol Cell Biol 2009;29:1375-1387.

INCB057643 Investigator's Brochure (IB). Wilmington, DE: Incyte Corporation.

Jakafi (ruxolitinib) [prescribing information]. Wilmington, DE: Incyte Corporation; 2016.

Jakavi (ruxolitinib) [summary of product characteristics]. Camberley, United Kingdom: Novartis Europharm Limited; 2017.

Kaminskas E, Farrell A, Abraham S, et al. Approval summary: azacitidine for treatment of myelodysplastic syndrome subtypes. Clin Cancer Res 2005;11:3604-3608.

Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous recombination deficiency: exploiting the fundamental vulnerability of ovarian cancer. Cancer Discov 2015;5:1137-1154.

Landskron G, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic inflammation and cytokines in the tumor microenvironment. J Immunol Res 2014;2014:149185.

Lilenbaum RC, Herndon JE 2nd, List MA, et al. Single-agent versus combination chemotherapy in advanced non–small cell lung cancer: the Cancer and Leukemia Group B (Study 9730).

Lord CJ, Ashworth A. PARP inhibitors: synthetic lethality in the clinic. Science 2017;355:1152-1158.

Lorusso D, Di Stefano A, Fanfani F, Scambia G. Role of gemcitabine in ovarian cancer treatment. Ann Oncol 2006;17:v188-v194.

Mesa RA, Gotlib J, Gupta V, et al. Effect of ruxolitinib therapy on myelofibrosis-related symptoms and other patient-reported outcomes in COMFORT-I: a randomized, double blind, placebo-controlled trial. J Clin Oncol 2013a;31:1285-1292.

Mesa RA, Shields A, Hare T, et al. Progressive burden of myelofibrosis in untreated patients: assessment of patient-reported outcomes in patients randomized to placebo in the COMFORT-1 study. Leuk Res 2013b;37:911-916.

Mochizuki K, Nishiyama A, Jang MK, et al. The bromodomain protein BRD4 stimulates G1 gene transcription and promotes progression to S phase. J Biol Chem 2008;283:9040-9048.

Mostaghel EA, Nelson PS. Intracrine androgen metabolism in prostate cancer regression: mechanisms of castration resistance and therapeutic implications. Best Pract Res Clin Endocrinol Metab 2008;22:243-258.

Mutch DG, Orlando M, Goss T, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol 2007;25:2811-2818.

National Comprehensive Cancer Network (NCCN). National Comprehensive Cancer Network Guidelines in Oncology Version 1.2017. 2017. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed October 2, 2017.

Nicodeme E, Jeffrey KL, Schaefer U, et al. Suppression of inflammation by a synthetic histone mimic. Nature 2010;468:1119-1123.

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenström macroglobulinaemia: update from the VIth International Workshop. Br J Haematol 2013;160:171-176.

Page ST, Lin DW, Mostaghel EA, et al. Persistent intraprostatic androgen concentrations after medical castration in healthy men. J Clin Endocrinol Metab 2006;91:3850-3856.

Perez EA, Vogel CL, Irwin DH, Kirshner JJ, Patel R. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol 2001;19:4216-4223.

Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non–small-cell lung cancer. J Clin Oncol 2012;30:3516-3524.

Pignata S, Lorusso D, Scambia G, et al. Pazopanib plus weekly paclitaxel versus weekly paclitaxel alone for platinum-resistant or platinum-refractory advanced ovarian cancer (MITO 11): a randomized, open-label, phase 2 trial. Lancet Oncol 2015;16:561-568.

Portela A, Esteller M. Epigenetic modifications and human disease. Nat Biotechnol 2010;28:1057-1068.

Poveda AM, Selle F, Hilpert F, et al. Bevacizumab combined with weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan in platinum-resistant recurrent ovarian cancer: analysis by chemotherapy cohort of the randomized phase III AURELIA trial. J Clin Oncol 2015;33:3836-3838.

Rubraca (rucaparib) [prescribing information]. Boulder, CO: Clovis Oncology; 2017.

Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomized, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015;16:152-160.

Savona MR, Malcovadi L, Komrokji R, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood 2015;125:1857-1865.

Sher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 2016;34:1402-1418.

Shimamura T, Chen Z, Soucheray M, Carretero J, et al. Efficacy of BET bromodomain inhibition in Kras-mutant non-small cell lung cancer. Clin Cancer Res 2013;19:6183-6192.

Siedman AD, Tiersten A, Hudis C, et al. Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. J Clin Oncol 1995;13:2575-2581.

Tang Y, Gholamin S, Schubert S, et al. Epigenetic targeting of Hedgehog pathway transcriptional output through BET bromodomain inhibition. Nat Med 2014;20:732-740.

Taxol (paclitaxel) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2011.

Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. Blood 2013;122:1395-1398.

Vannucchi AM, Kantarjian HM, Kiladjian JJ, et al. A pooled analysis of overall survival in COMFORT-I and COMFORT-II, 2 randomized phase III trials of ruxolitinib for the treatment of myelofibrosis. Haematologica 2015;100:1139-1145.

Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012;366:799-807.

Verstovsek S, Mesa RA, Gotlib J, et al. The clinical benefit of ruxolitinib across patient subgroups: analysis of a placebo-controlled, Phase III study in patients with myelofibrosis. Br J Haematol 2013;161:508-516.

Vidaza (azacitidine) [prescribing information]. Summit, NJ: Celgene Corporation; 2016.

Vidaza (azacitidine) [summary of product characteristics]. Uxbridge, United Kingdom: Celgene Europe Limited; 2017.

Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology Working Group. J Clin Oncol 2010;28:1963-1972.

Wilson AJ, Stubbs M, Liu P, et al. The bromodomain inhibitor INCB054329 enhances olaparib response in ovarian cancer cells by reducing homologous recombination efficiency. Presented at: American Association for Cancer Research(AACR) Special Conference onAddressing Critical Questions in Ovarian Cancer Research and Treatment; October 1-4, 2017; Pittsburgh, PA. Abstract B04.

Wu SY, Chiang CM. The double bromodomain-containing chromatin adaptor BRD4 and transcriptional regulation. J Biol Chem 2007; 282:13141-13145.

Wyce A, Degenhardt Y, Bai Y, et al. Inhibition of BET bromodomain proteins as a therapeutic approach in prostate cancer. Oncotarget 2013;4:2419-2429.

Yan J, Diaz J, Jiao J, Wang R, You J. Perturbation of BRD4 protein function by BRD4-NUT protein abrogates cellular differentiation in NUT midline carcinoma. J Biol Chem 2011;286:27663-27675.

Yang L, Zhang Y, Shan W, et al. Repression of BET activity sensitizes homologous recombination-proficient cancers to PARP inhibition. Sci Transl Med 2017;9:eeal1645.

Yasuda K, Igishi T, Kawasaki Y, et al. Phase II study of weekly paclitaxel in patients with non-small cell lung cancer who have failed previous treatments. Oncology 2004;66:347-352.

You JS, Jones PA. Cancer genetics and epigenetics: two sides of the same coin? Cancer Cell 2012;22:9-20.

Zatloukal P, Kanitz E, Magyar P, et al. Gemcitabine in locally advanced and metastatic non-small cell lung cancer: the Central European phase II study. Lung Cancer 1998;22:243-50.

Zytiga (abiraterone) [prescribing information]. Raritan, NJ: Janssen Pharmaceuticals, Inc; 2017a.

Zytiga (abiraterone) [summary of product characteristics]. Beerse, Belgium: Janssen-Cilag International NV; 2017b.

APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

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

Such methods include:

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

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

Source: CTFG 2014.

APPENDIX B. PHARMACOKINETIC ANALYTICAL PARAMETERS

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

In addition, the following PK parameters may be calculated, whenever possible, for each subject based on the urine INCB057643 concentrations:

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

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

APPENDIX C. EASTERN COOPERATIVE ONCOLOGYGROUP PEFORMANCE STATUS

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

Source: Oken et al 1982.

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

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

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

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

Source: Cheson et al 2003.

APPENDIX E. RESPONSE CRITERIA FOR GLIOBLASTOMA

RANO Criteria for Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; subjects must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Subjects with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Subjects with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids[a]; significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy[a] not cause by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

FLAIR = fluid-attenuated inversion recovery.
Note: Radiologic interpretation guidelines, definitions and tumor measurement instructions will be provided separately. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
[a] Stable doses of corticosteroids include subjects not on corticosteroids.
Source: Wen et al 2010.

Summary of the RANO Response Criteria

Criterion	CR	PR	SD	PD
T1 gadolinium disease	None	≥ 50% decrease	< 50% decrease but , 25% increase	≥ 25% increase[a]
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase[a]
New lesion	None	None	None	Present[a]
Corticosteroids	None	Stable or decrease	Stable or decrease	NA[b]
Clinical status	Stable or increase	Stable or increase	Stable or increase	Decrease[a]
Requirement for response	All	All	All	Any[a]

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; FLAIR = fluid-attenuated inversion recovery; NA = not applicable.

[a] Progression occurs when this criterion is present.

[b] Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

For purposes of this study, the minimum time from baseline for determination of SD will be 6 weeks.

Best overall response (BOR) should be determined based on response designations recorded per RANO defined criteria. The subject's BOR assignment will depend on the findings of both target and non-target disease, and will also take into consideration the appearance of new lesions.

The assessments that will contribute to the evaluation of BOR include the response assessment recorded between the date of randomization and the first to occur of the following:

1. The date of objectively documented progression per RANO criteria

   OR

2. The date of subsequent therapy

   OR

3. The date of pathology results from diagnostic surgical resection

Among the available response assessment, the criteria listed in the table below will be used to determine BOR.

Assessment of Best Overall Response

Best Overall Response	Criteria
Complete Response (CR)	CR observed in consecutive assessments ≥ 4 weeks apart per RANO
Partial Response (PR)	PR observed in consecutive assessments ≥ 4 weeks apart per RANO
Stable Disease (SD)[a]	SD observed and dose not quality for CR or PR Or Suspected PD followed with histologic results not confirming PD, and no CR, PR, or SD observed
Not Evaluable (NE)	Insufficient data to determine disease progression or response
Progressive Disease (PD)	No CR, PR, or SD before PD

[a] To qualify for SD there must be a minimum on-treatment period of 6 weeks.

In order to distinguish potential treatment-associated pseudoprogression from progressive disease and minimize premature discontinuation of study medication, subjects who initially meet radiologic criteria for disease progression but are believed to derive clinical benefit and are tolerating study medication should continue receiving study medication until confirmation of progression with a follow up MRI. Such subjects may be allowed to continue on study therapy for up to 12 additional weeks as long as they are no developing significant new or worsened neurologic deficits related to underlying tumor.

If the follow-up imaging after 12 weeks from initial tumor progression confirms further progression, the date of progression will be the date at which progression was first determined. For purposes of this study, the minimum duration between baseline (start of treatment) and first on-study scan in order to determine BOR of SD is 6 weeks. If the minimum time is not met when SD is otherwise the best timepoint response, the subject's best response will depend on the subsequent assessments. For example, a subject who has SD at a timepoint < 6 weeks and PD at a second assessment will have a best response of PD.

Subjects with a complete or partial response must have that response sustained for 4 weeks. Subjects who do not qualify for complete response, partial response, or confirmed progression will be considered as stable disease for the protocol BOR analysis.

APPENDIX F. INTERNATIONAL WORKING GROUP RESPONSE CRITERIA FOR MYELODYSPLASTIC SYNDROME

Category	Response Criteria (Responses Must Be at Least 4 Weeks in Duration)
Complete remission (CR)	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines Persistent dysplasia will be noted Peripheral blood: Hemoglobin (Hgb) ≥ 11 g/dL, Platelets ≥ 100×10^9/L, Neutrophils ≥ 1.0×10^9/L Blasts 0%
Partial remission (PR)	All CR criteria if abnormal before treatment, except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 weeks
Treatment failure	Death during treatment Disease progression characterized by worsening of cytopenias, increase in % of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Disease progression (PD)	For patients with: - Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts - 5%-10% blasts: ≥ 50% increase in blasts to > 10% blasts - 10%-20% blasts: ≥ 50% increase in blasts to > 20% blasts - 20%-30% blasts: ≥ 50% increase in blasts to > 30% blasts Any of the following: - At least 50% decrement from maximum remission/response levels in granulocytes or platelets - Reduction in Hgb concentration by ≥ 2 g/dL - Transfusion dependence
Disease transformation	Transformation to AML (30% or more blasts)
Relapse after CR or PR	At least 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. INTERNATIONAL CONSORTIUM PROPOSAL OF UNIFORM RESPONSE CRITERIA FOR MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS IN ADULTS

Response Subcategory	Response Criteria
Complete Remission (CR)	• Presence of all of the following improvements: • Bone marrow: ≤ 5% myeloblasts (including monocytic blast equivalent in case of chronic myelomonocytic leukemia) with normal maturation of all cell lines and return to normal cellularity* • Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤ Grade 1 fibrosis)† • Peripheral blood‡ - 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*
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 §
Partial Remission (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‖ 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‖ 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‖ 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.

* 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.

† 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.

‡ 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.

§ 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.

‖ 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.

Response Subcategory	Response Criteria
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* • < 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† Evidence of cytogenetic evolution‡ • 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 **Minor criteria:** • Transfusion dependence§ • 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 CBC. • Evidence of clonal evolution (molecular)¶

* Blasts as measured from the bone marrow.
† 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.
‡ 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.
§ 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.
¶ 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 H. REVISED RESPONSE CRITERIA FOR MYELOFIBROSIS: INTERNATIONAL WORKING GROUP-MYELOPROLIFERATIVE NEOPLASMS RESEARCH AND EUROPEAN LEUKEMIANET CONSENSUS REPORT

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

* Baseline and posttreatment bone marrow slides are to be interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.
† Grading of MF is according to the European classification.

‡ Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, < 5% immature myeloid cells is allowed.

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

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

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

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

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

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

Source: Tefferi et al 2013.

APPENDIX I. 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 J. CRITERIA FOR EVALUATING DISEASE RESPONSE AND PROGRESSION IN SUBJECTS WITH MULTIPLE MYELOMA TREATED BY HIGH-DOSE THERAPY AND HAEMOPOIETIC STEM CELL TRANSPLANTATION: MYELOMA SUBCOMMITTEE OF THE EUROPEAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION

Minimal Response	• ≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89%. • In addition to the above criteria, if present at baseline, 25% to 49% reduction in the size of soft tissue plasmacytomas is also required. • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).

Source: Blade et al 1998.

APPENDIX K. 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 1 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.

5PS = 5-point scale; LDi = longest transverse diameter of lesion; MRI = magnetic resonance imaging; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a] PET 5-point scale: 1, no uptake above background; 2, update ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Source: Cheson et al 2014.

APPENDIX L. RESPONSE ASSESSMENT IN WALDENSTRÖM MACROGLOBULINEMIA

Categorical Response Definitions in Waldenström Macroglobulinemia

Response Category	Response Definition
Complete response	• Absence of serum monoclonal IgM protein by immunofixation. • Normal serum IgM level. • Complete resolution of extramedullary disease, ie, lymphadenopathy and splenomegaly if present at baseline. • Morphologically normal bone marrow aspirate and trephine biopsy.
Very good partial response	• Monoclonal IgM protein is detectable ≥ 90% reduction in serum IgM level from baseline.[a] • Complete resolution of extramedullary disease, ie, lymphadenopathy/splenomegaly if present at baseline. • No new signs or symptoms of active disease.
Partial response	• Monoclonal IgM protein is detectable ≥ 50% but < 90% reduction in serum IgM level from baseline.[a] • Reduction in extramedullary disease, ie, lymphadenopathy/splenomegaly if present at baseline. • No new signs or symptoms of active disease.
Minor response	• Monoclonal IgM protein is detectable ≥ 25% but < 50% reduction in serum IgM level from baseline.[a] • No new signs or symptoms of active disease.
Stable disease	• Monoclonal IgM protein is detectable < 25% reduction and < 25% increase in serum IgM level from baseline.[a] • No progression in extramedullary disease, ie, lymphadenopathy/splenomegaly. • No new signs or symptoms of active disease.
Progressive disease	• ≥ 25% increase in serum IgM level[a] from lowest nadir (requires confirmation) and/or • Progression in clinical features attributable the disease.

[a] Sequential changes in IgM levels may be determined either by M-protein quantification by densitometry or total serum IgM quantitation by nephelometry.
Source: Owen et al 2013.

APPENDIX M. RESPONSE ASSESSMENT IN CHRONIC LYMPHOCYTIC LEUKEMIA

Complete Response (CR)

CR requires all of the following criteria as assessed:

1. Absence of clonal lymphocytes in the peripheral blood.
2. Absence of significant lymphadenopathy (eg, lymph nodes > 1.5 cm in diameter) by physical examination and in CT scan of the chest abdomen and pelvis.
3. No hepatomegaly or splenomegaly by physical examination and confirmed by CT scan.
4. Absence of constitutional symptoms.
5. Blood counts above the following values:
   a. Neutrophils > 1.5×10^9/L without the need exogenous growth factors.
   b. Platelets > 100×10^9/L without the need for exogenous growth factors.
   c. Hemoglobin > 110 g/L without the red blood cell transfusion or need for exogenous erythropoietin.
6. A marrow aspirate and biopsy should be performed if clinical and laboratory results listed in criteria 1 through 5 demonstrate that a CR has been achieved. The marrow should be assessed by flow cytometry and immunohistochemistry to demonstrate that the marrow is free of clonal B lymphocytes. If marrow is hypocellular a repeat marrow should be conducted in about 4 to 6 weeks provided criteria 1 through 5 are still satisfied.

Partial Response (PR)

To define a PR, the following parameters need to be documented for a minimum of 2 months' duration. Constitutional symptoms persisting for more than 1 month should be recorded.

1. A decrease in the number of blood lymphocytes by 50% or more from the values before therapy. Note: Persistent lymphocytosis should not interfere with the time of designation of a PR, which should be based more on the other measurable aspects of the disease than on lymphocytosis.
2. Reduction in lymphadenopathy by CT scan as defined by the following:
   a. A decrease in lymph node size by 50% or more in the sum products of up to 6 lymph nodes or in 1 lymph node diameter if only a single lymph node was present before therapy.
   b. No increase in any lymph node and no new enlarged lymph node. In small lymph nodes (< 2 cm) an increase of < 25% is not considered to be significant.
3. A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan (clinical studies) or palpation (general practice).

4. The blood count should show one of the following:
    a. Neutrophils > 1.5×10^9/L without the need for exogenous growth factors.
    b. Platelets > 100×10^9/L without the need for exogenous growth factors
    c. Hemoglobin > 11.0 g/dL without the red blood cell transfusion or need for exogenous erythropoietin.

Progressive Disease*

Progressive disease during or after therapy is characterized by at least one of the following that is confirmed with repeated observations and incorporates indicators of progressive disease that are not typically associated with tumor flare OR rely on indicators of progressive disease that do not resolve after use of measures to mitigate the signs or symptoms of tumor flare:

1. Lymphadenopathy:
    a. Appearance of any new lesion such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates.
    b. An increase by 50% or more in greatest determined diameter of any previous site. A lymph node of 1 to 1.5 cm must increase by 50% or more to a size greater than 1.5 cm in the longest axis. A lymph node of more than 1.5 cm must increase to more than 2.0 cm in the longest axis.
    c. An increase of 50% or more in the sum of the product of diameters of multiple nodes.
    d. Appearance of new lesions such as new lymphadenopathy (> 1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates.
2. An increase in the liver or spleen size by 50% or more or the *de novo* appearance of hepatomegaly or splenomegaly.
3. An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes/µL AND at least 1 sign or symptom of disease progression. Lymphocytosis alone should not be considered progressive disease.
4. Transformation to a more aggressive histology (eg, Richter syndrome). This diagnosis should be established by lymph node biopsy.
5. Occurrence of cytopenia (neutropenia, anemia or thrombocytopenia) attributable to CLL.

* Including modified criteria as referenced in Cheson et al 2012.

Stable Disease

Subjects who have not achieved a CR or a PR and who have not exhibited PD will be considered to have stable disease (which is equivalent to a nonresponse).

Source: Hallek et al 2008, Cheson et al 2012.

APPENDIX N. PROSTATE CANCER WORKING GROUP 3 GUIDELINES

Prostate Cancer Working Group 3 (PCWG3) guidelines (Sher et al 2016) will be used in this study for the following:

- Baseline disease assessments by the investigators, based on Table 2 (Table N1) in the PCWG3 guideline. Data will be collected through castration-resistant protein cancer (CRPC)-specific electronic case report form (eCRF) modules.
- Disease progression assessments by the investigators, based on blood-based PSA and imaging (nodes, viscera, and bone), as defined in Table 3 (Table N2) in the PCWG3 guideline. Data will be collected through CRPC-specific eCRF modules.
- Disease response assessments by the investigators, based on blood-based prostate-specific antigen testing and imaging (nodes, viscera, and bone) as defined in Table 5 (Table N3) in the PCWG3 guideline. Data will be collected through CRPC-specific eCRF modules.

Table N1: Standard Baseline Disease Assessments Recommended by PCWG3 in Comparison With PCGW2 Recommendations

Table 2. Standard Baseline Disease Assessments Recommended by PCWG3 in Comparison With PCWG2 Recommendations

Assessment	PCWG2 (2008)	PCWG3 (2015)
Histology	Not addressed	Adenocarcinoma Adenocarcinoma with small-cell or neuroendocrine features Small-cell carcinoma Report Gleason sum for primary Consider rebiopsy of metastatic disease
Clinical	History and physical examination	Age, pain, analgesic consumption, performance status, comorbidity assessment, history, and physical examination; prior local therapy; TNM stage at diagnosis; and PSA
Prior systemic treatment	Pre- and postchemotherapy	Record each line of systemic therapy (single agent or combination) in order of administration, including start and stop dates, dose(s), and schedule(s), the disease state in which it was administered, and response (resistant *v* sensitive) on the basis of PSA if appropriate Record type of progression on prior therapy (PSA, radiographic [bone, nodal, visceral], clinical [eg, pain escalation])
Prior radiation therapy	Not addressed	Site, administered dose per fraction and treatment duration
Blood-based biomarkers	PSA Testosterone	Host: CBC with differential, ALK, kidney/liver function, albumin, LDH, testosterone* Tumor: PSA and cPSA kinetics Optional: CEA, chromogranin A, neuron-specific enolase, CTC enumeration
Imaging		
Prostate/ prostate bed	Endorectal MRI	Retained, cross-sectional imaging of prostate region if applicable
Nodal	CT: Only nodes ≥ 2 cm were assessed for change in size	CT or MRI: Nodes ≥ 1.5 cm in the short axis are considered measurable; nodes ≥ 1.0 and less than 1.5 cm in the short axis are considered pathologic according to clinical discretion, and nontarget; nodes less than 1.0 cm in the short axis are nonpathologic Record pelvic and extrapelvic (retroperitoneal, mediastinal, thoracic, other) nodal disease separately; up to five nodes in total Record new lesions *v* growth of pre-existing lesions, and sites of new lesions
Visceral	CT: reported as visceral per RECIST	CT or MRI: Record individual sites of spread (lung, liver, adrenal, CNS) separately; up to five lesions per site Lesions ≥ 1.0 cm in the longest dimension are considered measurable Record new lesions *v* growth of pre-existing lesions, and sites of new lesions
Bone	^{99m}Tc MDP	Record new lesions and sites of new lesions
Tumor profiling for determinants of prognostic, predictive, and resistance biomarkers	Not addressed	Consider rebiopsy of metastatic or locally recurrent lesion(s) for biologic characterization
Patient-reported outcomes	None	Pain assessment, opiate analgesia consumption, physical functioning (functional status), health-related quality of life; consider fatigue and PRO-CTCAE. Validated PRO instruments strongly recommended

Abbreviations: ALK, alkaline phosphatase; CBC, complete blood count; CEA, carcinoembryonic antigen; CT, computed tomography; CTCs, circulating tumor cells; CTCAE, Common Terminology Criteria for Adverse Events; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; ^{99m}Tc MDP, ^{99m}Tc methylene diphosphonate.
*Ultrasensitive testosterone measures may be indicated where appropriate on the basis of drug under study and context.

Table N2: Criteria for Progression at Trial Entry by Disease Manifestation

Table 3. Criteria for Progression at Trial Entry by Disease Manifestation

Variable	PCWG2 (2008)	PCWG3 (2015)
Blood-based		
PSA	Obtain sequence of rising values at a minimum of 1-week intervals	Retained
	2.0 ng/mL minimal starting value	1.0 ng/mL is the minimal starting value if confirmed rise is only indication of progression unless pure small-cell carcinoma
	Estimate pretherapy PSADT if at least three values available ≥ 4 weeks apart	Retained
Imaging		
Nodes	Nodal progression sufficient for trial entry independent of PSA	Retained
	Measurable lesions not required for entry	Retained
	Use RECIST to record nodal lesions as target or nontarget	Modified RECIST 1.1 criteria, separate pelvic and extrapelvic disease, up to five nodal lesions total recorded
	Only lymph nodes ≥ 2 cm in diameter (long axis) were actionable as progressive disease	Previously normal (< 1.0-cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed
		If the node progresses to ≥ 1.5 cm in the short axis, it is measurable; nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable
		For existing pathologic adenopathy, progression is defined per RECIST 1.1
	Record presence of nodal and/or visceral disease separately	Retained with modification
		Nodal sites:
		Locoregional: pelvic only
		Extrapelvic: retroperitoneal, mediastinal, thoracic, or other
Viscera	Visceral progression sufficient for trial entry independent of PSA	Retained but recorded separately by site of spread (lung, liver, adrenal, CNS); up to five lesions per site of spread
	Measurable lesions not required for entry	Retained
	Use RECIST to record visceral lesions as target or nontarget	Retained
	Record presence of nodal and/or visceral disease separately	Retained with modification
		Visceral sites: lung, liver, adrenal, CNS
Prostate/prostate bed (primary site)	Record prior treatment of primary tumor	Retained
	Perform directed pelvic imaging (CT, MRI, PET/CT, endorectal MRI, transrectal ultrasound) to document presence or absence of disease	Retained
Bone	Two new lesions	Retained
	Confirm ambiguous results by other imaging modalities (eg, CT or MRI)	Retained, but only positivity on the bone scan defines metastatic disease to bone
Other sites of disease	Patients with treated epidural lesions and no other epidural progression are eligible	Retained
Type of progression at trial entry	Not addressed	Report separately:
		PSA only
		Bone only ± nodal disease
		Nodal disease only (no bone disease present)
		Visceral (lung, liver, adrenal, CNS) disease (± other sites)
		Record new lesions and site of new lesions *v* growth of pre-existing lesions, or both
Other markers		
Patient-reported outcomes	Not addressed	For pain palliation analyses, presence of clinically meaningful pain at baseline (eg, ≥ 4 on a 10-point pain intensity scale) is a prerequisite; for pain progression analyses, patients may have any level of pain at baseline, including no pain

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PET, positron emission tomography; PSA, prostate-specific antigen; PSADT, PSA doubling time; RECIST, Response Evaluation Criteria in Solid Tumors.

Table N3: Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer

Table 5. Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation

Variable	PCWG2 (2008)	PCWG3 (2015)
Histology	Not addressed	Encourage rebiopsy of metastatic sites or local recurrence at progression to evaluate for histologic (ie, neuroendocrine/small cell) transformation; in the context of clinical trials, encourage rebiopsy for biomarker assessment
Blood-based markers		
PSA	Recognize that a favorable effect on PSA may be delayed for ≥ 12 weeks, even for a cytotoxic drug	Retained
	Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression	Retained
	Ignore early rises (before 12 weeks) in determining PSA response	Retained
	For control/relieve/eliminate end points:	For control/relieve/eliminate end points:
	Record the percent change from baseline (rise or fall) at 12 weeks, and separately, the maximal change (rise or fall) at any time using a waterfall plot	Retained, except with timing (8-9 or 12 weeks) depending on trial design
		Separately report the proportion of patients who have undergone radical prostatectomy and achieved a nadir less than 0.2 ng/mL vprimary radiation therapy–treated patients who achieved a nadir less than 0.5 ng/mL
		Describe absolute changes in PSA over time from baseline to best response
	For delay/prevent end points (progression):	For delay/prevent end points (progression):
	After decline from baseline: record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value ≥ 3 weeks later (ie, a confirmed rising trend); the requirement for an increase of 5 ng/mL was decreased to 2 ng/mL, and the requirement for a 50% increase was reduced to 25%	Retained (standards for reporting PSA progression data may not indicate a need to stop treatment)
	Recording the duration of PSA decline of little value	Retained
	No decline from baseline: PSA progression ≥ 25% increase and ≥ 2 ng/mL increase from baseline beyond 12 weeks	Relate to mechanism of drug and anticipated timing of potential favorable/unfavorable effects on PSA, if present
CTC	Not addressed	Enumerate at the start of treatment: Record as favorable (four or fewer cells per 7.5 mL of blood) or unfavorable (five or more cells per 7.5 mL)
		If unfavorable, monitor for changes after treatment
		For control/relieve/eliminate end points:
		Report as change from unfavorable (five or more cells per 7.5 mL of blood) to favorable (four or fewer cells per 7.5 mL) and separately, the percent change from baseline using a waterfall plot
		For delay/prevent end points: no validated definition exists (however, rising CTC counts are associated with a poor prognosis)
LDH, total alkaline phosphatase, bone-specific alkaline phosphatase, urine *N*-telopeptide, hemoglobin, NLR	Not addressed	Descriptively report changes over time, may include the proportion showing normalization of a given biomarker and/or waterfall plots of percent change from baseline in a given biomarker
		Report institutional normal ranges to determine normalization of a given biomarker
Imaging biomarkers: nodal and visceral		
For control/relieve/eliminate end points		
General	Record changes in nodal sites separately from visceral sites	Record changes in lymph nodes, lung, liver, adrenal, and CNS sites separately

(continued on following page)

Table 5. Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation (continued)

Variable	PCWG2 (2008)	PCWG3 (2015)
	Use RECIST with caveats:	Record up to five lesions per site of disease
	Record changes in size using waterfall plot	Use RECIST 1.1 with caveats:
	Confirm favorable change with second scan	Record changes in size using waterfall plot
	Record complete elimination of disease at any site separately	Confirm favorable change with second scan
		Record complete elimination of disease at any site separately
Nodes	Only report changes in lymph nodes that were ≥ 2 cm in the long axis at baseline	Only report changes in lymph nodes that were ≥1.5 cm in the short axis
		Record changes in pelvic (regional) nodes *v* extrapelvic (distant/metastatic) nodes separately
Visceral	Use RECIST with caveats above	Use RECIST 1.1 with caveats:
		Record changes in liver, lung, adrenal, and CNS separately
		Only report changes in lesions ≥ 1.0 cm in the longest dimension
For delay/prevent end points		
Nodal and visceral	Use RECIST criteria for progression, with additional requirement that progression be confirmed by a second scan ≥ 6 weeks later (the second scan is particularly important when anticipated effect on PSA is delayed, or for biologic therapies)	General:
		Record changes in nodal and visceral (lung, liver, adrenal, and CNS) disease separately
		Use RECIST 1.1 but clearly record type of progression (growth of existing lesions *v* development of new lesions) separately by site
		The recommendations apply to both nmCRPC and mCRPC
		Record up to five lesions per site of spread
		Report the proportion who have not progressed at fixed time points (6 or 12 months)
	Note that for some treatments, a lesion may increase in size before it decreases	Retained
Nodal	As above	Previously normal (< 1.0-cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed
		Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable
		For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1
Imaging biomarkers: bone		
Metastatic	For control/relieve/eliminate end points:	For control/relieve/eliminate end points:
	Record changes as improved or stable (no new lesions) or worse (new lesions)	Retained with addition of resolved bone lesion
	Changes in intensity of uptake alone do not constitute progression or regression	Retained
	No new lesions: continue therapy in absence of other signs of progression	Retained
	New lesions (See Progression below)	Retained
	For delay/prevent end points (progression):	For delay/prevent end points (progression):
	Progression:	Progression:
	Exclude pseudoprogression in the absence of symptoms or other signs of progression	Retained
	At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)	
	If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented	Retained

(continued on following page)

Table 5. Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation (continued)

Variable	PCWG2 (2008)	PCWG3 (2015)
	For all scans after the first post-treatment scan, at least two new lesions	For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan
	Date of progression is the date of the scan that first documents the second lesion	Retained
	Changes in intensity of uptake alone do not constitute either progression or regression	Retained
		Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
nmCRPC	Not addressed	Nonmetastatic to metastatic progression: Any new unequivocal bone lesion, except if that lesion appears in the first post-treatment scan; in that case, document the event, continue treatment until 2 additional new lesions appear, and record both events
Patient-reported outcomes	Consider independently of other outcome measures	Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥ 4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use)
	For control/relieve/eliminate end points: Document pain and analgesia at entry with a lead-in period and measure repeatedly at 3- to 4-week intervals	For control/relieve/eliminate end points: Serial (eg, daily × 7 days) assessments at each time point can improve the stability of values
	Perform serial assessments of global changes in HRQoL, urinary or bowel compromise, pain management, additional anticancer therapy	Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement
	Ignore early changes (≤ 12 weeks) in pain or HRQoL in absence of compelling evidence of disease progression	
	For delay/prevent end points: Confirm response or progression of pain or HRQoL end points ≥ 3 weeks later	For delay/prevent end points: Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use)
		Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later)
		Time to deterioration of physical function and/or HRQoL scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire

Abbreviations: CTC, circulating tumor cell; HRQoL, health-related quality of life; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; NLR, neutrophil/lymphocyte ratio; nmCRPC, nonmetastatic castration-resistant prostate cancer; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PRO, patient-reported outcome; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.

APPENDIX O. CYP3A4 INHIBITORS AND INDUCERS

University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org. Accessed October 2017.

Yellow highlighted rows indicate changes from the last database update in July 2017.

In Vivo CYP3A Inhibitors

SCHOOL OF PHARMACY
UNIVERSITY of WASHINGTON
Drug Interaction Database Program

In Vivo Inhibitors of CYP3A Probes

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate AUCr > 5)						
VIEKIRA PAK[2]	Antivirals	See note[2]	tacrolimus[2]	55.76	25708713	2015 May
indinavir /RIT	Protease Inhibitors	800/100 mg BID (1 day)	alfentanil	36.5	19225389	2009 Mar
tipranavir/RIT	Protease Inhibitors	500/200 mg BID (2 days)	midazolam	26.91	20147896	2010 Jun
ritonavir	Protease Inhibitors	3 doses of 100 mg over 24 h	midazolam	26.41	20002087	2009 Dec
cobicistat (GS-9350)	None	200 mg QD (14 days)	midazolam	19.03	20043009	2010 Mar
indinavir	Protease Inhibitors	800 mg TID (7 days)	vardenafil	16.25	NDA # 021400	2003 Aug
ketoconazole	Antifungals	400 mg QD (4 days)	midazolam	15.9	8181191	1994 May
troleandomycin	Antibiotics	500 mg single dose	midazolam	14.8	15536460	2004 Dec
telaprevir	Antivirals	750 mg TID (16 days)	midazolam	13.5	22162542	2012 Oct
danoprevir / RIT	Antivirals	200/100 mg QD (14 days)	midazolam	13.42	23872824	2013 Nov
elvitegravir / RIT	Treatments of AIDS	150/100 mg QD (10 days)	midazolam	12.8	NDA # 203100	2012
saquinavir / RIT	Protease Inhibitors	1000/100 mg BID (14 days)	midazolam	12.48	19792991	2009 Oct
lopinavir / RIT	Protease Inhibitors	400/100 mg BID (2 days)	alfentanil	11.47	24067429	2013 Dec
itraconazole	Antifungals	200 mg QD (4 days)	midazolam	10.8	8181191	1994 May
voriconazole	Antifungals	200 mg BID (9 days)	midazolam	9.63	21937987	2011 Nov
mibefradil	Calcium Channel Blockers	100 mg single dose	midazolam	8.86	14517191	2003 Oct
LCL161	Cancer Treatments	600 mg single dose	midazolam	8.8	23585187	2013 Jun
clarithromycin	Antibiotics	500 mg BID (7 days)	midazolam	8.39	16432272	2006 Feb
posaconazole	Antifungals	400 mg BID (7 days)	midazolam	6.23	19302901	2009 Feb
telithromycin	Antibiotics	800 mg QD (6 days)	midazolam	6.2	NDA# 021144	2004
grapefruit juice DS[3]	Food Products	240 mL TID (2 days) and 90 min, 60 min, 30 min prior to midazolam	midazolam	5.95	12953340	2003 Aug
conivaptan	Diuretics	40 mg BID (5 days)	midazolam	5.76	NDA # 021697	2005
nefazodone	Antidepressants	100-200 mg BID (12 days)	midazolam	5.44	14551182	2003 Nov
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)	midazolam	5.29	21406602	2011 Jun
saquinavir	Protease Inhibitors	1200 mg TID (5 days)	midazolam	5.18	10430107	1999 Jul
idelalisib	Kinase Inhibitors	150 mg BID (8 days)	midazolam	5.15	25760671	2015 Aug
boceprevir	Antivirals	800 mg TID (6 days)	midazolam	5.05	NDA # 202258	2011
Moderate CYP3A Inhibitors (AUCr ≥ 2 and < 5)						
erythromycin	Antibiotics	1000 mg single dose	midazolam	4.99	25139487	2014 Dec
fluconazole	Antifungals	400 mg single dose	midazolam	4.93	16172184	2005 Oct
atazanavir / RIT	Protease Inhibitors	300/100 mg BID	maraviroc	4.9	18333863	2008 Apr
darunavir	Protease Inhibitors	1200 mg BID (14 days)	saquinavir	4.9	NDA # 021976	2006
diltiazem	Calcium Channel Blockers	60 mg TID (2 days)	midazolam	4.06	21209240	2011 Nov
darunavir / RIT	Protease Inhibitors	400/100 mg BID (8 days)	sildenafil	4.0	NDA # 021976	2006
dronedarone	Antiarrhythmics	400 mg BID (14 days)	simvastatin	3.66	NDA # 022425	2009
crizotinib	Kinase Inhibitors	250 mg BID (28 days)	midazolam	3.65	NDA # 202570	2011
atazanavir	Protease Inhibitors	400 mg QD (7 days)	maraviroc	3.57	18333863	2008 Apr
GSK2647544	Alzheimer's Disease & Dementia Treatments	80 mg BID (7 days)	simvastatin	3.3	27719741	2016 Dec
aprepitant	Antiemetics	80-125 mg QD (5 days)	midazolam	3.29	12891225	2003 Aug
casopitant	Antiemetics	120 mg QD (14 days)	midazolam	3.13	20840445	2010 Oct
amprenavir	Protease Inhibitors	1200 mg BID (10 days)	rifabutin	2.93	11158747	2001 Feb
faldaprevir	Antivirals	240 mg BID (14 days)	midazolam	2.92	25449227	2015 Apr
imatinib	Antineoplastic Agents	400 mg QD (7 days)	simvastatin	2.92	14612892	2003 Nov
verapamil	Calcium Channel Blockers	80 mg TID (2 days)	midazolam	2.92	8198928	1994 Mar
netupitant	Antiemetics	300 mg single dose	midazolam	2.44	23729226	2013 Oct
nilotinib	Kinase Inhibitors	400 mg BID (12 days)	midazolam	2.4	25418605	2015 Apr
grapefruit juice	Food Products	240 mL QD (4 days)	midazolam	2.39	10546919	1999 Oct
tofisopam	Benzodiazepines	100 mg TID (9 days)	midazolam	2.36	17989974	2008 Jan
cyclosporine	Immunosuppressants	Not provided (1-5 years)	midazolam	2.21	21753749	2011 Sep

SCHOOL OF PHARMACY
UNIVERSITY of WASHINGTON
Drug Interaction Database Program

In Vivo Inhibitors of CYP3A Probes

ACT-178882	Renin Inhibitors	300 mg QD (14 days)	midazolam	2.19	22849770	2013 Dec
ciprofloxacin[4]	Antibiotics	500 mg single dose	sildenafil	2.12	16372380	2005 Dec
schisandra sphenanthera	Herbal Medications	3 capsules (= 11.25 mg deoxyschizandrin) BID (7 days)	midazolam	2.05	19552749	2009 May
isavuconazole	Antifungals	200 mg TID (11 days)	midazolam	2.03	27273461	2016 Jun
cimetidine	H-2 Receptor Antagonists	200-400 mg QID (1.5 days)	midazolam	2.02	6152615	1984 Sep
FK1706	Central Nervous System Agents	60 mg QD (14 days)	midazolam	2.01	19889885	2010 Feb
		Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2)				
tabimorelin	Hormone Replacement	2.86-3.21 mg QD (7 days)	midazolam	1.93	12610745	2003 Feb
amlodipine	Calcium Channel Blockers	5 mg QD (4 days)	simvastatin	1.93	28350522	2017 Apr
ranolazine	Cardiovascular Drugs	1000 mg BID (7 days)	simvastatin	1.89	NDA # 021526	2006
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 (Citrus aurantium) juice	Food Products	240 mL single dose	felodipine	1.76	11180034	2001 Jan
amiodarone	Antiarrhythmics	400 mg QD (4 days)	simvastatin acid	1.76	17301736	2007 May
chlorzoxazone	Muscle Relaxants	250 mg single dose (part of a 6-drug cocktail)	midazolam	1.68	11736864	2001 Nov
M100240	Antihypertensive Agents	50 mg single dose	midazolam	1.66	15051745	2004 Apr
fluvoxamine	Antidepressants	50-00 mg BID (12 days)	midazolam	1.66	14551182	2003 Nov
ranitidine	H-2 Receptor Antagonists	150 mg BID (1.5 days)	midazolam	1.66	6135440	1983 Jun
fostamatinib[5]	Anti-inflammatory Drugs	100 mg BID (7 days)	simvastatin	1.64	26748647	2016 Mar
goldenseal	Herbal Medications	1,323 mg (= 24.1 mg isoquinoline alkaloids) TID (14 days)	midazolam	1.63	17495878	2008 Jan
clotrimazole	Antifungals	10 mg TID (5 days)	midazolam	1.61	20233179	2010 Feb
tacrolimus	Immunosuppressants	Not provided (1-5 years)	midazolam	1.61	21753749	2011 Sep
palbociclib	Kinase Inhibitors	125 mg QD (8 days)	midazolam	1.58	NDA # 207103	2015
cilostazol	Antiplatelets	100 mg BID (7 days)	lovastatin	1.56	10702889	1999
ticagrelor	Antiplatelets	180 mg bid (7 days)	simvastatin	1.56	NDA # 022433	2011
peppermint oil	Food Products	600 mg (= 300 uL peppermint oil) single dose	felodipine	1.55	12235445	2002 Sep
ivacaftor	Cystic fibrosis treatments	150 mg BID (6 days)	midazolam	1.54	25103957	2015 Jan
GSK2248761	Transcriptase Inhibitors	100 mg QD (12 days)	midazolam	1.54	22288567	2012 Aug
Guan Mai Ning	Herbal Medications	3 tablets TID (7 days)	simvastatin	1.51	25801058	2015 Sep
osilodrostat	Adrenal Steroidogenesis Inhibitors	50 mg single dose	midazolam	1.49	28155129	2017 May
AZD2327	Depression Treatments	15 mg QD (7 days)	midazolam	1.49	26081137	2015 Nov
piperine	Food Products	20 mg QD (10 days)	carbamazepine	1.48	27776366	2017 Jan
resveratrol	Food Products	500 mg QD (10 days)	carbamazepine	1.48	25624269	2015 May
roxithromycin	Antibiotics	300 mg QD (6 days)	midazolam	1.47	7995324	1994
suvorexant	Hypnotics - Sedatives	80 mg QD (14 days)	midazolam	1.47	NDA # 204569	2014
propiverine	Anticholinergics	15 mg BID (7 days)	midazolam	1.46	16183781	2005 Dec
isoniazid	Antibiotics	90 mg BID (4 days)	triazolam	1.46	6140941	1983 Dec
berberine	Herbal Medications	300 mg TID (14 days)	midazolam	1.45	21870106	2012 Feb
oral contraceptives	Oral contraceptives	OC with low doses of estrogen (< 35 ug ethinylestradiol) (> 3 months)	triazolam	1.44	6149030	1984 Nov
delavirdine	NNRTIs	400 mg TID (9 days)	indinavir	1.44	9665503	1998 Jul
daclatasvir	Antivirals	60 mg QD (7 days)	simeprevir	1.44	NDA # 205123	2013
simeprevir	Protease Inhibitors	150 mg QD (11 days)	midazolam	1.43	NDA # 205123	2013
atorvastatin	HMG CoA Reductase Inhibitors (Statins)	10-40 mg/day (chronic treatment)	midazolam IV	1.41	12911366	2003 Sep
tolvaptan	Vasopressin Antagonists	60 mg single dose	lovastatin	1.41	NDA # 022275	2009
almorexant	Hypnotics - Sedatives	200 mg QD (9 days)	midazolam	1.37	22990330	2013 Mar
GSK1292263	Other Antilipemics	300 mg BID (9 days)	simvastatin	1.36	23256625	2013 Jun
evacetrapid	CETP inhibitors	300 mg QD (15 days)	midazolam	1.35	26264702	2015 Dec
linagliptin	Dipeptidyl Peptidase 4 Inhibitors	10 mg QD (6 days)	simvastatin	1.34	20497745	2010 Jun
grazoprevir *(ingredient of Zepatier)*	Antivirals	200 mg QD (7 days)	midazolam	1.34	NDA # 208261	2016
lacidipine	Calcium Channel Blockers	4 mg QD (8 days)	simvastatin	1.33	11259986	2001 Feb
cranberry juice	Food Products	240 mL double strength juice, 1 glass q 15 min x 3	midazolam	1.33	19114462	2009 Mar

SCHOOL OF PHARMACY
UNIVERSITY of WASHINGTON
Drug Interaction Database Program

In Vivo Inhibitors of CYP3A Probes

pazopanib	Kinase Inhibitors	800 mg QD (17 days)	midazolam	1.32	20881954	2010 Nov
everolimus	Immunosuppressants	10 mg QD (5 days)	midazolam	1.31	23426978	2013 Apr
blueberry juice	Food Products	two doses of 300 mL, separated by 16 hours	buspirone	1.31	22943633	2013 Apr
flibanserin	Central Nervous System Agents	50 mg BID (4 days)	simvastatin	1.31	NDA # 022526	2015
brodalumab	Immunomodulators Biologics	210 mg single dose subcutaneously	midazolam	1.3	NDA # 761032	2017
AMD070	Fusion Inhibitors	200 mg BID (8 days)	midazolam	1.29	18362694	2008 Apr
alprazolam	Benzodiazepines	1 mg TID (7 days)	buspirone	1.29	8300893	1993 Nov
Tong Xin Luo	Herbal Medications	4 capsules TID (7 days)	simvastatin	1.29	25801058	2015 Sep
bicalutamide	Antiandrogens	150 mg QD (>3 months)	midazolam	1.27	15509184	2004
sitaxentan	Endothelin Receptor Antagonists	100 mg QD (7 days)	sildenafil	1.27	20078609	2010 Jan
azithromycin	Antibiotics	500 mg QD (3 days)	midazolam	1.27	8720318	1996 Feb
obeticholic acid	Miscellaneous Agents	25 mg QD (13 days)	midazolam	1.26	NDA # 207999	2016
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

Notes:

[1] To allow better comparability, DDI studies with the probe substrate midazolam were selected first. When no study with midazolam was available, the AUCratio of another probe or sensitive substrate is presented.

[2] VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days. Tacrolimus is also a substrate of OATP1B1/1B3 that can be inhibited by Viekira Pak.

[3] 240 mL GFJ double-strength administered TID for 3 days

[4] Of note, co-administration of ciprofloxacin (750 mg BID for 7 days) did not affect plasma concentrations of ivacaftor, which is also a sensitive substrate for CYP3A (KALYDECO Prescribing Information).

[5] Fostamatinib also inhibits BCRP, and BCRP inhibition likely participates to the increase in exposure of simvastatin

[6] Brodalumab indirectly inhibits CYP3A through regulation of cytokines

In Vivo CYP3A Inducers

SCHOOL OF PHARMACY
UNIVERSITY of WASHINGTON
Drug Interaction Database Program

In Vivo CYP3A Inducers

Inducers	Therapeutic class	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Dose (oral)	PMID or NDA #	Published
Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%))							
rifampin	Antibiotics	budesonide	99.7	36904.5	600 mg QD (7 days)	15726657	2005 Mar
mitotane	Other Antineoplastics	midazolam	94.5	Not Provided	maximum of 3.5 g TID (chronic therapy)	21220434	2011 Apr
avasimibe	Other Antilipemics	midazolam	93.5	Not Provided	750 mg/day (7 days)	12766253	2003 Sep
phenytoin	Anticonvulsants	nisoldipine	89.5	Not Provided	200-450 mg/day (chronic treatment)	8917062	1996 Nov
carbamazepine	Anticonvulsants	quetiapine	86.6	643.1	200 mg TID (26 days)	16390352	2006 Jan
enzalutamide	Antiandrogens	midazolam	85.9	Not Provided	160 mg QD (85±3 days)	NDA # 203415	2012
St John's Wort extract	Herbal Medications	midazolam	80.0	Not Provided	300 mg TID (14 days)	16341856	2006 Jan
lumacaftor	Cystic Fibrosis Treatments	ivacaftor	80.0	Not Provided	not provided	NDA # 206038	2015
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
dabrafenib	Kinase Inhibitors	midazolam	74.1	Not Provided	150 mg BID (repeated dosing)	NDA # 202806	2013
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
PF-06282999	Myeloperoxidase Inactivators	midazolam	57.2	Not Provided	500 mg BID (14 days)	28254951	2017 May
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
telotristat ethyl	Antidiarrheals	midazolam	50.6	83.0	500 mg QD (5 days)	NDA # 208794	2017
Weak Inducers (AUC decreased by 20-50% or CL increased by 20-100% (less than 2 fold))							
eslicarbazepine	Anticonvulsants	simvastatin	49.4	98.4	800 mg QD (14 days)	23726291	2013 Sep
telaprevir	Antivirals	darunavir	48.4	Not Provided	1125 mg BID (4 days)	NDA# 201917	2011
garlic	Food Products	saquinavir	44.7	Not Provided	caplet of GarliPure BID (20 days)	11740713	2002 Jan
bexarotene	Other Antineoplastics	atorvastatin	45.3	Not Provided	400 mg/m2 QD (at least two 4-week cycles)	22057855	2012 Feb
sarilumab***	Immunomodulators Biologics	simvastatin	43.2	Not Provided	200 mg single dose subcutaneously	27722854	2017 Jun
artesunate and mefloquine	Antimalarials	lopinavir	43.1	75.4	4 mg/kg QD artesunate on Days 1-3 + 750 mg mefloquine on Day 1 and 500 mg on	26452725	2015
amprenavir (fosamprenavir)	Protease Inhibitors	lopinavir	43.0	Not Provided	700 mg BID (2-4 weeks)	15668539	2005 Jan
raltegravir	HIV-Integrase Strand Transfer Inhibitors	darunavir	42.0	Not Provided	400 mg BID	21958880	2012 Feb
lesinurad	Antigout and Uricosuric Agents	amlodipine	41.9	72.5	400 mg QD (24 days)	NDA # 207988	2015
vemurafenib	Kinase Inhibitors	midazolam	39.4	Not Provided	960 mg BID (15 days)	NDA # 202429	2011
troglitazone	Thiazolidinediones	simvastatin	37.7	Not Provided	400 mg QD (24 days)	11361054	2001 May
sorafenib	Kinase Inhibitors	sirolimus	36.9	Not Provided	200 mg BID (11 days)	21045832	2010 Nov
rufinamide	Anticonvulsants	triazolam	36.7	53.4	400 mg BID (11.5 days)	NDA # 021911	2008
sirukumab***	Immunomodulators Biologics	midazolam	35.7	Not Provided	300 mg single dose subcutaneously	26054042	2015 Dec
pleconaril	Antivirals	midazolam	34.6	52.8	400 mg TID (6 days)	16467135	2006 May
ginseng	Herbal Medications	midazolam	34.2	50.7	500 mg BID (28 days)	21646440	2012 Jun
boceprevir	Antivirals	darunavir	34.2	41.0	800 mg every 8 hrs (6 days)	23155151	2013 Mar
sulfinpyrazone	Antigout and Uricosuric Agents	cyclosporine	33.9 (change in C_{ss})		200 mg/day	11124491	2000 Dec
ginkgo	Herbal Medications	midazolam	33.7	52.6	120 mg BID (28 days)	18205997	2008 Feb
vinblastine	Vinca Alkaloids	midazolam IV	33.2	48.8	not provided (4 cycles)	20959500	2010 Nov
nevirapine	NNRTIs	indinavir	32.5	Not Provided	200 mg QD (14 days), then BID (19 days)	10191212	1999 May

SCHOOL OF PHARMACY
UNIVERSITY of WASHINGTON
Drug Interaction Database Program

In Vivo CYP3A Inducers

armodafinil (R-modafinil)	Psychostimulants	midazolam	32.2	54.7	100-250 mg/day (31 days)	18076219	2008
ticagrelor	Anticoagulants and Antiplatelets	midazolam	31.7	46.5	400 mg QD (6 days)	23870610	2013 Jul
LCL161	Cancer Treatments	midazolam	29.8	34.0	600 mg single dose	23585187	2013 Jun
vicriviroc and ritonavir	Treatments of AIDS	ethinyl estradiol	29.4	Not Provided	30 mg vicriviroc and 100 mg ritonavir QD (10 days)	22015327	2011 Oct
ritonavir	Protease Inhibitors	ethinyl estradiol	29.2	Not Provided	100 mg QD (10 days)	22015327	2011 Oct
prednisone	Corticosteroids	tacrolimus	29.0	Not Provided	1.5 mg/kg/day	15787787	2005 Apr
oxcarbazepine	Anticonvulsants	felodipine	28.1	Not Provided	450 mg BID (7 days)	8451779	1993 Feb
danshen	Herbal Medications	midazolam	27.9	32.8	4 g TID (14 days)	20565457	2010 Jun
clobazam	Benzodiazepines	midazolam	27.7	Not Provided	40 mg QD (15 days)	22422635	2012 Apr
echinacea	Herbal Medications	midazolam	27.3	37.5	500 mg TID (28 days)	20653355	2010 Aug
ticlopidine	Anticoagulants and Antiplatelets	alfentanil	27.0	50.0	250 mg BID (4 days)	23361846	2013 Mar
isavuconazole	Antifungals	lopinavir	27.0	Not Provided	not provided (clinical dose)	NDA # 207500	2015
brivaracetam	Anticonvulsants	ethinyl estradiol	26.8	37.3	200 mg BID (21 days)	24386664	2013 Dec
Stribild*	Treatments of AIDS	ethinyl estradiol	26.2	31.3	150 mg ELV + 150 mg COB + 200 mg EMT+ 300 mg TEN	NDA # 203100	2012
pioglitazone	Thiazolidinediones	midazolam	26.0	Not Provided	45 mg QD 7 days	Actos® Product Label	2004 Aug
VIEKIRA PAK**	Antivirals	darunavir	25.7	Not Provided	See note**	NDA # 206619	2014
dexamethasone	Corticosteroids	aprepitant	25.0	Not Provided	8 mg/day (5 days)	NDA # 021549	2003
terbinafine	Antifungals	midazolam	24.5	Not Provided	250 mg QD (4 days)	8527290	1995 Sep
quercetin	Food Products	midazolam	23.6	Not Provided	500 mg QD (13 days)	21680781	2012 Jun
glycyrrhizin	Herbal Medications	midazolam	23.0	Not Provided	150 mg BID (15 days)	20393696	2010 Aug
aprepitant	Neurokinin-1 Receptor Antagonists	midazolam IV	22.1	28.5	125/80 mg QD (3 days)	14973304	2004 Mar
pretomanib (PA-824)	Antibiotics	midazolam	22.1	20.7	400 mg QD (14 days)	23689718	2013 Aug
oritavancin	Antibiotics	midazolam	18.7	23.9	1200 mg IV single infusion	NDA # 206334	2014
AZD 7325	Anxiolytics	midazolam	18.7	22.6	10 mg QD (12 days)	22122233	2012 Jul
methylprednisolone	Corticosteroids	cyclosporine	15.8	35.0	16 mg/day (12 days) then 8 mg/day (6 months)	12164891	2002 Sep
topiramate	Anticonvulsants	ethinyl estradiol	12.0	20.2	50 mg/day (21 days)	12681003	2003 Apr

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

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

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

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

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

APPENDIX P. SCREENING SYMPTOM FORM

Instructions to Subjects: Please answer all questions to the best of your ability, based on your memory **over the past 7 days (1 week)**. There is no right or wrong answer.

1. During the past 7 days, how severe were your worst night sweats (or feeling hot or flushed) due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
2. During the past 7 days, how severe was your worst itchiness due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
3. During the past 7 days, how severe was your worst abdominal discomfort (feel uncomfortable, pressure or bloating) due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
4. During the past 7 days, how severe was your worst pain under the ribs on the left side due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
5. During the past 7 days, what was the worst feeling of fullness (early satiety) you had after beginning to eat, due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
6. During the past 7 days, how severe was your worst bone or muscle pain due to MF (diffuse, not joint or arthritis pain)?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
7. During the past 7 days, what was the worst degree of inactivity (including work and social activities) you had due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Investigators/Site Staff:

Please complete the table below to confirm the criterion used to confirm the subject's eligibility in the trial based on an assessment of his/her active symptoms of myelofibrosis.

ELIGIBILITY CRITERION	CONFIRMATION
A symptom score of at least 5 on at least 1 of the symptoms	□ Yes □ No
A symptom score of 3 or greater on at least 2 of the symptoms	□ Yes □ No

APPENDIX Q. MANAGEMENT OF POTENTIAL HY'S LAW CASES

INTRODUCTION

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's law (PHL) criteria at any point during the study.

The investigator participates, in conjunction with Incyte clinical project and pharmacovigilance representatives, in the review and assessment of cases fulfilling PHL criteria to ascertain whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug.

The investigator fulfils requirements for the recording of data pertaining to PHL or Hy's law cases and adverse event (AE)/serious adverse event (SAE) reporting according to the outcome of the review and assessment in line with standard safety reporting processes.

ACTIONS REQUIRED FOR REPEAT EPISODES OF AST OR ALT > 3 × ULN AND/OR TOTAL BILIRUBIN > 2 × ULN

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

If the alternative cause for the previous occurrence of PHL was not chronic or progressing malignant disease, please follow the process for PHL review and assessment as described in this appendix.

If the alternative cause for the previous occurrence of PHL was chronic or progressing malignant disease, please follow the instructions below:

- Determine if there has been a significant change* in the subject's condition.
  - If there is no significant change, no action is required.
  - If there is a significant change, follow the process described for PHL review and assessment as described in this appendix.

* A 'significant' change in the subject's condition refers to a clinically relevant change in ALT, AST, or total bilirubin, or associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

DEFINITIONS

For the purpose of this process definitions are as follows

Potential Hy's Law

An increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × upper limit of normal (ULN) and total bilirubin > 2 × ULN at any point during the study. The elevations do not have to be at the same time or within a specified timeframe.

Hy's Law

An increase in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN where no other reason can be found to explain the combination of increases, for example, elevated serum alkaline phosphatase (ALP) indicating cholestasis, viral hepatitis, another drug.

ACTIONS REQUIRED IN CASES OF AST OR ALT > 3 × ULN OR TOTAL BILIRUBIN ≥ 2 × ULN

Identification and Determination of Potential Hy's Law

To identify cases of AST or ALT > 3 × ULN or total bilirubin > 2 × ULN and consequently determine whether the subject meets PHL criteria, please follow the instructions below:

- Review the laboratory report, and if a subject has AST or ALT > 3 × ULN OR total bilirubin > 2 × ULN at any visit, then proceed as follows:
  - Determine without delay whether the subject meets PHL criteria by reviewing laboratory reports from all previous visits.
  - Enter the laboratory data into the laboratory case report form (CRF) as soon as possible.

Potential Hy's Law Criteria Not Met

If the subject has NOT had AST or ALT > 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Perform follow-up on subsequent laboratory results according to the guidance provided in Section 5.4.2 of the Protocol.

Potential Hy's Law Criteria Met

If the subject has had AST or ALT > 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instructions below:

- Have subject interrupt study drug.
- Notify Incyte study team without delay.
  - The investigator, or designee, should contact the medical monitor to discuss and agree upon an approach for the study subject's follow-up and the continuous review of data.
- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as medically indicated.
- Investigate the etiology of the event and perform any relevant diagnostic investigations as discussed with the medical monitor.
- Enter the laboratory data into the laboratory CRF as soon as possible.

- If at any time (in consultation with the medical monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

REVIEW AND ASSESSMENT

No later than 3 weeks after the biochemistry abnormality was initially detected and the criteria for PHL were met, the medical monitor, Incyte pharmacovigilance physician, and investigator will discuss and review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug. Subject matter experts will be included in the review as appropriate.

Evaluation of Alternative Causes

In order to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, the following alternative etiologies should be considered, including, but not limited to, the following:

- Active viral hepatitis
- Alcoholic and autoimmune hepatitis
- Hepatobiliary disorders
  - Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.
- Concomitant treatment
- Other causes such as systemic infections (bacterial, fungal, viral), nonalcoholic steatohepatitis, and cardiovascular diseases

Actions After Review and Assessment

According to outcome of the review and assessment, please follow the instructions below:

If there **is** an agreed alternative explanation for the AST or ALT **and** total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE.

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF if possible.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the CRF accordingly and follow the standard study processes.
- Have subject resume study drug as per Protocol guidelines.

If it is agreed that there is no explanation that would explain the AST or ALT and total bilirubin elevations, then proceed as follows:

- Have the subject permanently discontinue study drug and perform end-of-treatment procedures.

- Report an SAE (report term "Hy's Law").
  - The "medically important" serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the Hy's law case, a causality assessment of "related" should be assigned.
- If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for a Hy's law case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made. Report an SAE (report term "Potential Hy's Law") applying serious criteria and causality assessment as per above.

Source: FDA 2009.

APPENDIX R. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	18 JAN 2016
Amendment (Version) 2:	08 JUL 2016
Amendment (Version) 3:	14 MAR 2017
Amendment (Version) 4:	07 JUN 2017
Amendment (Version) 5:	11 OCT 2017
Amendment (Version) 6:	06 MAY 2018
Amendment (Version) 7:	22 OCT 2018

Amendment 7 (22 OCT 2018)

Overall Rationale for the Amendment:

The primary purpose of Protocol Amendment 7 is to remove the disease status follow-up and survival follow-up for subjects who end study treatment. Disease assessments will also be conducted per investigator discretion.

This amendment includes the changes to Protocol INCB 57643-101 Amendment 6 (06 MAY 2018) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. [redacted] **Section 4.1, Overall Study Design; Section 7.6.2, Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score; Section 7.6.3, Patient Global Impression of Change; Section 9.4.1.2, Secondary Efficacy Analyses; [redacted]; Appendix Q, Patient Global Impression of Change; Appendix R, Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score.**

   Description of change: Part 4 will not open in Amendment 7.

   Rationale for change: This study was placed on screening and enrollment hold in MAR 2018, and no further subjects will be entered onto the study; therefore, Part 4 will not open (see Section 1.6.2).

2. **Synopsis; Section 5.5.2, Withdrawal Procedures; Section 6, Study Assessments; Section 6.4.2, Disease Status Follow-Up; Section 6.4.3, Survival Follow-Up (Part 2 and Part 4 Only); Section 7.7, Efficacy Assessments; Section 7.10.2, Data Collection for Survival Follow-Up**

   Description of change: Disease status follow-up and survival follow-up will not be required after end of study treatment in Amendment 7. Efficacy and disease assessments will be conducted at the discretion of the investigator.

   Rationale for change: No further development of INCB057643 will be conducted after these subjects end study treatment; therefore, follow-up will not be collected. Investigators may keep the subject on study treatment if they believe that the subject is receiving clinical benefit and the subject agrees by re-consenting; therefore, the investigator may follow efficacy and disease assessments at their own discretion.

3. **Section 7.5.4.1 Twelve-Lead Electrocardiograms**

   Description of change: With Amendment 7, local ECGs will not be collected by a central vendor.

   Rationale for change: All subjects currently on study treatment have passed the serial ECG part of the study; therefore, ECGs that have clinically significant findings per the investigator may be collected as adverse events.

4. **Section 7.5.5.1, Chemistry, Hematology, Urinalysis, Coagulation Panel, Factor VII, Serology, and Endocrine Function Testing**

   Description of change: The investigative site will not enter local laboratory results into the eCRF with Amendment 7. Abnormal laboratory values that are considered clinically significant adverse events should be entered into the eCRF as an adverse event.

   Rationale: In order to reduce site burden, only abnormal laboratory values that are considered clinically significant will be entered into the eCRF as adverse events.

5. **Section 1.5.1, Preclinical Safety and Risks; Section 1.6, Clinical Experience With INCB057643 in Study INCB 57643-101**

   Description of change: Preclinical safety and risks as well as clinical experience during the INCB 57643-101 study were updated.

   Rationale: These sections were updated with emerging data.

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

Amendment 6 (06 MAY 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is add new preclinical safety data and cardiac monitoring assessments.

1. **Section 1.5.1, Preclinical Safety and Potential Risks**

   Description of change: Updated to include safety data from a 3-month monkey study.

   Rationale for change: To provide updated data.

2. **Section 5.4.2, INCB057643 Dose Interruptions and Reductions (Table 8)**

   Description of change: Guidelines for study drug interruption/discontinuation for cardiac toxicities were added to Table 8.

   Rationale for change: Guidance on cardiac toxicity needed based on updated preclinical safety data.

3. **Section 6, Study Assessments (Schedule of Assessment Tables 10, 12, 15, 18, 21, 24, and 27); Section 7.5.4.4, Echocardiogram or MUGA**

   Description of change: Echocardiogram or MUGA assessment was added.

   Rationale for change: Cardiac monitoring added based on updated preclinical safety data.

4. **Section 6, Study Assessments (Laboratory Assessment Tables 11, 13, 16, 19, 22, 25, 28, and 31); Section 7.5.5.4, Cardiac Troponin (Either T or I) Testing**

   Description of change: Cardiac troponin (either T or I) testing was added.

   Rationale for change: Cardiac monitoring added based on updated preclinical safety data.

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

The following revisions from Administrative Change 3 (dated 23 MAR 2018) were also incorporated:

6. **Section 5.3, Treatment Compliance**

   Description of change: The following statement was added: "Drug accountability will not be captured in InForm for standard of care agents used in this study."

   Rationale for change: To correct an inadvertent omission.

7. **Section 6, Study Assessments (Tables 11, 12, 14, 15, 26, and 27)**

   Description of changes:

   - For Tables 11, 12, 14, and 15, where Cycle 1 and Cycle 2 are combined under 1 column, a ± 3-day evaluation window was added for Cycle 2 Day 1 only.

- For Table 26 and Table 27, where all cycles are combined under 1 column, a ± 2-day evaluation window was added for Cycle 2 Day 1 and subsequent cycles.

Rationale for changes: To clarify and to update for consistency.

8. **Section 6, Study Assessments (Tables 9, 10, 17, 18, 20, 21, 23, and 24)**

   Description of change: A footnote was added to the Day 11 cell to indicate that after a subject has been on study for 6 months, Day 11 visits at subsequent cycles will be optional at the discretion of the investigator.

   Rationale for change: To decrease the number of visits for subjects who are clinically stable without clinically significant AEs.

9. **Section 6, Study Assessments (Tables 10, 12, 15, 18, 21, 24, and 27)**

   Description of changes:

   - Table 10, footnote e was updated to indicate that sampling does not need to be repeated on Day 11 of Cycle 3 or any subsequent cycles; however, it should be performed any time there is a Grade 2 increased INR.
   - Tables 10 (footnote e), 12 (footnote d), 15 (footnote d), 18 (footnote e), 21 (footnote d), 24 (footnote d), and 27 (footnote f) were updated to indicate that *study visits* do not need to be delayed waiting on the Factor VII protein/antigen assay results as long as INR/PT results are within normal limits.
   - Tables 18, 21, and 24 weree updated to remove the following statement from footnote d, which does not apply: "Coagulation panel is also sampled on C1D2."

   Rationale for changes: To clarify and/or to correct an error.

10. **Section 6, Study Assessments (Table 12)**

    Description of change: Timed PK plasma assessment was removed.

    Rationale for change: To correct an error, as Table 12 currently indicates that timed PK assessments need to be obtained in Cycle 2. This is not correct and contradicts Table 13, which details timed PK assessments separately.

11. **Section 6, Study Assessments (Tables 12, 24, and 27)**

    Description for change: A serum pregnancy test at safety follow-up was added.

    Rationale for change: To correct an error.

12. **Section 6, Study Assessments (Tables 13, 16, 19, 22, and 28)**

    Description of changes: The collection of serial PK sampling should be conducted after INCB057643 administration. In Tables 13, 16, 19, 22, and 28, footnote a was revised to specify "INCB057643 administration" instead of "drug administration."

    Rationale for changes: To clarify timing of PK sampling, as the purpose of the serial PK sampling in combination therapy cohorts is to assess whether the standard of care agent will affect INCB057643 PK.

13. **Section 6, Study Assessments (Table 17 and Table 23)**

    Description of change: Disease assessments was added at end of treatment.

    Rationale for change: To correct an error.

14. **Section 7.8.1, Blood Sample Collection**

    Description of change: Fasting restrictions were updated to reflect that subjects do not need to refrain from water for 8 hours before or 1 hour after any PK sampling.

    Rationale for change: It is not necessary to refrain from water before or after PK sampling.

Amendment 5 (11 OCT 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to add dose-finding and dose-expansion cohorts to evaluate INCB057643 in combination with select standard of care (SOC) agents in advanced malignancies and to update aspects of the monotherapy design based on emerging data from the current study.

This amendment includes the changes to Protocol INCB 57643-101 Amendment 4 (Version 4 dated 07 JUN 2017) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 1, Introduction; Section 2, Study Objectives and Endpoints; Section 3, Subject Eligibility; Section 4, Investigational Plan; Section 5, Treatment; Section 6, Study Assessments; Section 7, Conduct of Study Assessments and Procedures; Section 9, Statistics; Section 11, References; Appendix N, Prostate Cancer Working Group 3 Guidelines; Appendix P, Screening Symptom Form; Appendix Q, Patient Global Impression of Change; Appendix R, Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score; Appendix S, Management of Potential Hy's Law Cases**

   Description of change: The study design was revised to include 6 combination INCB057643 and SOC dose-finding cohorts (ie, INCB057643 in combination with gemcitabine, paclitaxel, rucaparib, abiraterone plus prednisone, ruxolitinib, and azacitidine) and 4 combination INCB057643 and SOC dose-expansion cohorts (ie, INCB057643 in combination with rucaparib, abiraterone plus prednisone, ruxolitinib, and azacitidine). All relevant Protocol sections, including tables, figures, and appendices, were either added or revised accordingly. Study objectives and endpoints were revised in consideration of combination therapy.

   Rationale: To provide the background, rationale, study design, study objectives/endpoints, inclusion/exclusion criteria, treatment details, study assessments, and statistical considerations necessary in order to research INCB057643 in combination with SOC regimens in advanced malignancies.

2. **Synopsis; Section 3.1, Subject Inclusion Criteria; Section 4.1.2, Part 2 – Monotherapy Dose Expansion (Figure 1); Section 9.2, Selection of Sample Size**

   Description of change: Ewing's sarcoma tumor type was added to Part 2 Monotherapy Dose Expansion.

   Rationale for change: In a model of Ewing sarcoma, expressions of fusion transcription factors caused by the translocation of EWS and ETS genes results in global epigenetic reprogramming. These changes are associated with the expression of an oncogenic program that characterizes Ewing sarcoma. Treatment of Ewing cell lines with BET inhibitors was shown to block EWS-ETS dependent transcription and to reduce the growth of these cells and tumors *in vitro* and *in vivo*. These data suggest a therapeutic role for BET inhibitors across a wide range of cancers and demonstrate that neoplasms derived from aberrant activity of lineage-determining transcription factors may be

particularly responsive. Therefore, Ewing sarcoma was added to Part 2 Treatment Group A for further exploration in the clinical setting.

3. **Synopsis; Section 3.2, Exclusion Criteria; Section 5.7.1, Restricted Medications**

   Description of change: Coagulation criteria were added to increase surveillance of coagulation factors, particularly for subjects who are taking coumarin-based anticoagulants, such as warfarin. Investigators will be asked to consider switching subjects from warfarin to an alternate anticoagulation therapy that does not directly target Factor VII. Bleeding considerations were added to the exclusion criteria for subjects experiencing clinically significant bleeding within 14 days of Cycle 1 Day 1.

   Rationale for change: A subject experienced a Grade 4 event of increased international normalized ratio while taking INCB057643 and warfarin; therefore, stricter monitoring on coagulation laboratory values was added. Thrombocytopenia was found to be a dose limiting toxicity; and, therefore, subjects who are at a high risk for bleeding will be excluded from this study.

4. **Section 1.6, Clinical Experience With INCB057643 in Study INCB 57643-101**

   Description of change: The clinical pharmacokinetics and clinical study experience were revised to include emerging data from ongoing analyses.

   Rationale for change: To provide an update on the emerging data in INCB057643 monotherapy.

5. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment, including the addition of the summary of changes for all amendments to Appendix T.

Amendment 4 (07 JUN 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to revise the exclusion criterion for inadequate organ function based on FDA comments.

This amendment includes the changes to Protocol INCB 57643-101 Amendment 3 (14 MAR 2017) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 1.4, INCB057643 Preclinical Safety and Potential Risks; Section 3.2, Subject Exclusion Criteria**

   Description of change: Exclusion criteria 2d was revised to indicate that subjects in both Part 1 and Part 2 will be excluded if creatinine clearance is < 50 mL/min based on Cockroft-Gault formula or 24-hour urinalysis (< 30 mL/min for multiple myeloma). Pharmacokinetic data were added to Section 1.4.

   Rationale for change: The pharmacokinetics of INCB057643 was characterized in rats, dogs, and monkeys. The urinary excretion of INCB057643 was determined to be 12.5% of dose in monkeys, 17.6% in rats, and 26.1% in dogs. Further, *in vitro* and *in vivo* metabolism studies in animals indicate generation of major and minor metabolites. These data indicate that renal clearance is not the major route of clearance for INCB057643 and that metabolism is likely the predominant clearance pathway. The clearance mechanism of the active metabolite, INCB057228, is less clear; however, exposure of this metabolite in patients is only about 10% to 15% of parent.

   Enrollment of patients with mild to moderate organ impairment (≤ G2 creatinine clearance) in the carefully monitored Phase 1 setting would allow us to better understand the impact of such organ dysfunction on the disposition of INCB057643 and in turn would inform the inclusion/exclusion criteria for Phase 2 studies.

   Upon further consideration, the threshold for creatinine clearance for both Parts 1 and 2 will be the same (ie, exclusion of subjects with creatinine clearance < 50 mL/min based on Cockroft-Gault formula or 24-hour urinalysis and < 30 mL/min for subjects with multiple myeloma).

Amendment 3 (14 MAR 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to amend the definition of pharmacologically active dose (PAD), treatment group population, number of subjects, maximum tolerated dose (MTD), dose-limiting toxicity (DLT), study assessments, including coagulation laboratory monitoring, and inclusion/exclusion criteria.

This amendment includes the changes to Protocol INCB 57643-101 Amendment 2 (08 JUL 2016) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 3, Subject Eligibility; Section 4, Investigational Plan; Section 5.4.1, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose (Table 3: Definition of Dose-Limiting Toxicity)**

   Description of changes:

   - The PAD definition of plasma concentration exceeding *ex vivo* or projected c-Myc IC_{50} for approximately 12 hours has been modified to "for approximately 6-12 hours or achieves clinical response."
   - The following language was added: The sponsor along with the investigator may now elect to investigate 1 or more dose levels less than the nontolerated dose (NTD) or expand a dose cohort(s) deemed tolerable up to 12 subjects in order to obtain additional pharmacokinetic (PK), pharmacodynamic (PD), and safety data before determining the MTD.
   - Singular or nonfasting elevations in blood glucose ≥ Grade 3 will not be considered DLTs; blood glucose excursions will be considered DLTs if fasting blood glucose is ≥ Grade 3 on 2 separate occasions and 3 days apart.
   - For Part 1 Dose Escalation and Part 2 Dose Expansion, Treatment Group B (TGB) was revised to add 'acute' to leukemia as well as myelodysplastic syndrome/myeloproliferative neoplasms (MDS/MPN), or myelofibrosis (MF); MDS/MPN and MF were removed from Treatment Group C (TGC).
   - In Part 2 Dose Expansion, the following tumor types were removed from Treatment Group A (TGA): colorectal cancer, non−small cell lung cancer, and NUT midline carcinoma.
   - The number of subjects has been increased to 255. Part 1 will include up to approximately 60 subjects. In Part 2 TGA, the number of subjects has increased from 60 to 120. The pancreatic adenocarcinoma, breast cancer, glioblastoma multiforme, and non-Hodgkin's lymphoma groups will enroll 5 to 15 subjects; the additional group (any solid tumor or lymphoma with aberrations in Myc or other genes in which BET proteins are relevant) will enroll up to 20 subjects. The high-grade serous ovarian cancer group will include approximately 20 subjects. At least 5 of these will have BRD4 amplification, and another 5 will have MYC amplification/overexpress/translocation. The BRD4 and MYC molecular signature will be identified either by known status before subject screening or retrospectively after subject enrollment. The castration-resistant prostate cancer group will include

approximately 20 subjects. At least 5 of these will have androgen receptor splice variant 7 (AR-V7), and another 5 will have neuroendocrine phenotype. The AR molecular signature will be identified either by known status before subject screening or retrospectively after subject enrollment. Part 2/TGB will enroll approximately 5 to 15 subjects for each of the 4 tumor types (up to 60 subjects), and Part 2/TGC will enroll initially 5 to 15 subjects with MM.

Rationale for changes: Based on preclinical, PK, and emerging safety data, the PAD, tumor target types, number of subjects, and DLT criteria were refined.

2. Synopsis; Section 3, Subject Eligibility

Description of changes:

- In inclusion criterion 3a (prior therapy for Parts 1 and 2/TGA and TGB), the following statements were added: Subjects with AML are eligible if they have relapsed and/or refractory disease; if they are ≥ 65 years of age and are not candidates for or have refused standard chemotherapy, or if they have no established standard of care that is known to provide clinical benefit in the judgement of the investigator. Subjects with MF must be resistant, refractory, or intolerant to ruxolitinib therapy. Epithelial ovarian cancer was changed to high-grade serous ovarian cancer.
- In inclusion criterion 4, the timeframe of pretreatment tumor biopsy was clarified to be preferably ≤ 1 year old.
- In exclusion criterion 2, the following clarifications were added for inadequate organ function status:
  - Total bilirubin > 1.5 × ULN is acceptable if direct bilirubin ≤ 1.2 × ULN or with a diagnosis of Gilbert's syndrome.
  - Creatinine clearance was differentiated for Part 1 and Part 2. The original language is assigned to Part 1 and reads as follows: Creatinine clearance < 50 mL/min based on Cockroft-Gault formula or 24-hour urinalysis (< 30 mL/min for MM). Part 2 states creatinine clearance < 40 mL/min based on Cockroft-Gault formula or 24-hour urinalysis (< 30 mL/min for MM).
- Exclusion criterion 3d (receipt of anticancer medication) was revised to < 4 weeks for immunotherapy *or antibody therapy*. The following statements were also added:
  - Low-dose corticosteroids (prednisone or the equivalent ≤ 10 mg per day) may be administered.
  - Hydroxyurea should not be used within at least 48 hours before and on the day of the [redacted] sample collection [redacted].
  - For Parts 1 and 2/TGC: Receipt of less than 160 mg dexamethasone within 14 days before receiving the first dose of study drug is allowed.
  - Denosumab and zoledronic acid are permitted to treat cancer-related bone diseases.
- Exclusion criterion 11 was changed to Type 1 diabetes or uncontrolled Type 2 diabetes, and a required exclusion criterion 11b has been added to include that HbA1c of ≥ 8% at screening will exclude a subject.

- Exclusion criterion 15 relating to brain or central nervous system metastases has been revised to state that subjects with glioblastoma are not subjected to this criterion with medical monitor approval.
- Exclusion criterion 17 was revised to indicate a history of cardiac condition of ≤ 1 year. A statement was also add that subjects with a pacemaker and well-controlled rhythm for at least 1 month before first dose of study drug will be allowed.
- Exclusion criterion 27 was added to exclude subjects with any sign of clinically significant bleeding.

Rationale for changes: The inclusion and exclusion criteria was modified either due to emerging safety data or to provide clarity.

3. **Section 1.5, Clinical Experience With INCB057643 in Study INCB 57643-101**

   Description of change: Preliminary PK and safety data from the current study were added.

   Rationale for change: To provide investigators with current clinical data.

4. **Section 5.6, Concomitant Medications**

   Description of change: The following statements were added to restricted medications:

   - Subjects with glioblastoma may be treated with corticosteroids (prednisone or equivalent) > 10 mg/day with approval from the medical monitor.
   - Additional timed PK testing following the schedule for Cycle 1 Day 15 may be required if subjects initiate or require a dose adjustment of inhibitors or inducers of CYP3A4 during the study.
   - Use of anticoagulants that will increase the INR, such as coumarin-based anticoagulants (eg, warfarin), is discouraged, but not prohibited. Coagulation panel should be monitored more closely while a subject is on any anticoagulant.
   - Hydroxyurea for controlling proliferative disease is permitted with medical monitor approval, but should not be used within 48 hours before and on the day of PD sample collection.

   The following statements were added to prohibited medications:

   - Denosumab and zoledronic acid are permitted to treat cancer-related bone diseases.
   - Use of potent inducers and inhibitors of CYP3A4 (see Appendix N) *with the exception of certain topical medications such as ketoconazole, based on its low overall bioavailability*.

   Rationale for changes: Revised due to emerging safety data and to provide clarity.

5. Section 6, Study Assessments (Tables 5-7); Section 6.4.3, Survival Follow-Up; Section 7.5.5.2, Pregnancy Testing; Section 7.5.5.3, Hepatitis Screening Tests; Section 7.8.2, Urine Sample Collection

Description of changes:

- In Table 5, triplicate ECGs revised to include 0.5-, 6-, and 8-hour timepoints to match serial PK sampling. A statement was added to obtain the triplicate ECGs with a 1- to 3-minute break between evaluations.
- In Table 5 footnote h, a statement was added to obtain bone marrow disease assessments during Cycle 2 unless contraindicated.
- In Table 6, weekly (Cycle 1 Day 1, Day 2, Day 8, and Day 15) coagulation panel was added during Cycle 1. For subjects who experience a treatment-emergent increased INR/PT, a Factor VII concentration is requested along with the coagulation panel for Cycle 1 Day 1, Cycle 1 Day 15, and as needed.
- The following statements were added to Table 6: Screening laboratory tests must be performed within 14 days before Cycle 1 Day 1. Serum chemistry and hematology may be omitted on Cycle 1 Day 1 if completed within 3 days before Cycle 1 Day 1. If the screening serum pregnancy test was completed within 3 days before Cycle 1 Day 1, a urine pregnancy test may be performed on Cycle 1 Day 1.
- Table 6 and Section 7.8.2 revised to indicate that when a PK urine sample is collected, a predose void should be collected and recorded.
- Table 7 revised to include HbA1c at screening.
- Table 7 and Section 7.5.5.3 revised to indicate that hepatitis B and C viral loads by PCR assay only need to be assessed when respective serology results are positive. Hepatitis B virus DNA does not need to be performed if the surface antibody is the only positive result.
- In Section 6.4.3, a time frame of up to 2 years was added for survival follow-up.

Rationale for change: Based on emerging safety data, HbA1c at screening and more frequent monitoring of the coagulation panel were added. The other statements are clarifications or corrections.

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

Amendment 2 (08 JUL 2016)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to amend the dose-limiting toxicity criteria.

This summary of changes includes the changes to Protocol INCB 57643-101 Amendment 1 (15 MAY 2016) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

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

   Description of change: Nonhematologic toxicity was defined as any ≥ Grade 3 nonhematologic toxicity except nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. This has now been amended to define nonhematologic toxicity as any ≥ Grade 3 toxicity except nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours; any nonhematologic toxicity clearly and incontrovertibly related to the underlying disease or its progression; alopecia; and Grade 3 fatigue, asthenia, fever, anorexia, or constipation.

   Rationale for change: This is a first-in-human Phase 1 protocol to test an agent in subjects with advanced malignancies. The patient population often have very advanced disease and have had multiple of lines of treatment and, as a result, often have multiple persistent physical symptoms such as fatigue and pain. Those symptoms are often Grade 1 or Grade 2 at enrollment, and the severity/grades often fluctuate, especially at the time of disease progression. Declaring a toxicity as a DLT when it's clearly associated with the underlying disease or disease progression will seriously hinder the ability to test an anticancer agent in the clinic to meet an unmet medical need.

Amendment 1 (18 JAN 2016)

Overall Rationale for the Amendment:

The primary objectives of this amendment are to remove Part 3 of the study, to add stopping rules for unacceptable toxicity observed during the dose-expansion portion, and to update the dose-limiting toxicity (DLT) and dose interruption/reduction criteria.

This amendment includes changes to Protocol INCB 57643-101 (17 DEC 2015) as summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 1, Introduction; Section 2, Study Objectives and Endpoints; Section 3, Subject Eligibility; Section 4, Investigational Plan; Section 5, Treatment; Section 6, Study Assessments; Section 7, Conduct of Study Assessments and Procedures; Section 8, Safety Monitoring and Reporting; Section 9, Statistics; Section 11, References**

   Description of change: Part 3 of the study was removed.

   Rationale: Change requested by FDA.

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

   Description of change: Revised Exclusion Criterion #2a to include total bilirubin levels only.

   Rationale: Change requested by FDA.

3. **Synopsis; Section 4.1.2, Part 2 - Dose Expansion**

   Description of change: Stopping criteria were added to the dose-expansion portion (Part 2) of the study.

   Rationale: Change requested by FDA.

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

   Description of change: The DLT definition was updated to remove references to investigator attribution.

   Rationale: Change requested by FDA.

5. **Section 5.4.2, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose; Table 1**

   Description of change: The DLT definition for thrombocytopenia was updated to include ≥ Grade 3 events associated with bleeding or any requirement for platelet transfusion in all treatment groups.

   Rationale: Change requested by FDA.

6. **Section 5.4.6, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug; Table 2**

   Description of change: Guidelines for toxicity management were updated to remove any consideration of investigator attribution.

   Rationale: Change requested by FDA.

7. **Section 5.4.6, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug; Table 2**

   Description of change: Guidelines for toxicity management were updated to recommend interruption of study drug for Grade 3 events and recovery to ≤ Grade 1 prior to resumption of dosing at the next lower dose level; guidelines for Grade 4 events were updated to require discontinuation from the study. An exception for hematologic toxicities without clinical consequence (eg, no fever, infection, bleeding) was added.

   Rationale: Change requested by FDA.

8. **Section 6, Study Assessments; Table 3, Schedule of Assessments – Part 1 and Part 2**

   Description of change: Timepoints for drug dispensing and compliance check were updated.

   Rationale: To clarify appropriate timepoints for dispensing of drug and monitoring of study drug compliance.

9. **Section 6, Study Assessments; Table 3, Schedule of Assessments – Part 1 and Part 2**

   Description of change: Footnote "d" was updated as follows: "Triplicate ECGs will be performed predose and 1, 2, and 4 hours postdose on both Cycle 1 Day 1 and Cycle 1 Day 15." The X indicating ECG assessment on Cycle 1 Day 8 was deleted.

   Rationale: To provide consistency with the Protocol-required timepoints for triplicate ECGs.

Signature Manifest

Document Number: IC-DEV-PROT-AMEND-0403 **Revision:** 0

Title: INCB 57643-101 Protocol Amendment 7

All dates and times are in Eastern Standard Time.

57643-101 Protocol Am 7

Approval and Release

Name/Signature	Title	Date	Meaning/Reason
[redacted]	[redacted]	22 Oct 2018, 03:35:28 PM	Approved
[redacted]	[redacted]	22 Oct 2018, 04:04:32 PM	Approved
[redacted]	[redacted]	23 Oct 2018, 11:36:54 AM	Approved
[redacted]	[redacted]	23 Oct 2018, 04:32:15 PM	Approved