Clinical Study Protocol

INCB 54329-101 / NCT02431260

Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB054329 in Subjects With Advanced Malignancies

Product:	**INCB054329**
IND Number:	**124,657**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-off** **Wilmington, DE 19803**
Date of Protocol:	**21 JAN 2015**
Date of Amendment 1:	**01 JUL 2015**
Date of Amendment 2:	**08 DEC 2016**

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

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for INCB054329. I have read INCB 54329-101 Protocol Amendment 2 (dated 08 DEC 2016) 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: INCB054329

Title of Study: Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB054329 in Subjects With Advanced Malignancies

Protocol Number: INCB 54329-101	**Study Phase:** 1/2

Primary Objectives:

- To evaluate the safety and tolerability of INCB054329 in subjects with advanced malignancies.

Secondary Objectives:

- To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of INCB054329 in subjects with advanced malignancies.
- To evaluate preliminary efficacy of INCB054329 in subjects with advanced malignancies.

[redacted]

Overall Study Design:

This is an open-label, dose-escalation study of the bromodomain extra-terminal (BET) inhibitor INCB054329 in subjects with advanced malignancies. Subjects will receive once-daily (QD) doses of INCB054329 in 21-day cycles until withdrawal criteria are met (eg, toxicity, disease progression). The study will be conducted in 3 parts:

- Part 1 Dose Escalation will determine the maximum tolerated dose (MTD) of INCB054329 and/or a tolerated dose that reaches the desired target inhibition (ie, a pharmacologically active dose [PAD]).
- Part 2 Dose Titration will determine the feasibility of intrasubject dose titration using Protocol-defined criteria.
- Part 3 Dose Expansion will evaluate the doses and schedules selected in Part 1and Part 2 in subjects with select tumor types postulated to be particularly susceptible to BET inhibition (see inclusion criteria).

<u>Part 1 Dose Escalation</u>

The study will begin with open-label dose escalation in TGA, using a 3 + 3 design to determine the tolerated dose over a 21-day cycle. Initially, subjects in Cohort 1 will receive a single dose of INCB054329 followed by a timed PK assessment to confirm exposure approximately 1 week before continuous administration is initiated. The starting dose for continuous administration will be determined based on the exposures assessed at this PK assessment; this dose will be no higher than 15 mg.

The dose-escalation portion of the study will be conducted in the following treatment groups:

- Treatment Group A (TGA) will include subjects with any advanced solid tumor or lymphoma.
- Treatment Group B (TGB) will include subjects with acute leukemia, myelodysplastic syndrome (MDS), myelodysplastic/myeloproliferative neoplasms (MDS/MPN), and myelofibrosis (MF).

Escalation will begin with Cohort 1 (including the Day 0 single-dose PK assessment) in TGA; TGB will begin enrollment at the PAD (plasma concentration exceeding the PK which is projected to inhibit c-Myc level $\geq$ 50% for approximately 10 hours) or a tolerated dose identified in TGA at the discretion of the sponsor, and dose escalation will proceed independently to an MTD in each treatment group using a 3 + 3 design. Treatment Group C will open in Part 2 instead of Part 1. Alternative dose regimens may be explored such as twice-daily (BID) or intermittent dose regimens, pending emerging PK, PD, and safety

data. 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, the next cohort will begin enrollment at the next highest dose level. Dose increases between cohorts may be up to 2-fold until a Grade 2 toxicity is observed, after which dose increases will be limited to no more than 50% above the previous level. If 1 DLT is observed in the first 3 subjects in a cohort, 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, $\geq$ 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 that at which one-third or more of subjects in a particular cohort report DLTs. If the Cohort 1 dose is not tolerated ($\geq$ 2 of 6 subjects report a DLT), a dose de-escalation will be considered.

If a PAD is reached before identifying the MTD, the PAD may be selected for use in the expansion cohort, at the discretion of the sponsor.

Individual subjects within each cohort will undergo reductions/interruptions in INCB054329 administration according to prescribed safety parameters.

Part 2 Dose Titration

Part 2 will enroll 2 treatment groups to investigate the feasibility of intrasubject dose titration with Protocol-defined criteria. Part 2 TGA will enroll advanced solid tumors and lymphomas; Part 2 TGC will enroll multiple myeloma (MM). The starting dose will be the highest tolerated dose with continuous BID dose administration identified in Part 1 TGA. At the end of Cycle 1, if dose titration criteria are met, the dose may be increased to 25 mg BID on Day 1 of Cycle 2. Dose escalation by $\leq$ 5 mg BID increments may be permitted after each subsequent cycle of treatment if the subject continues to meet the dose escalation criteria. Dose interruptions, reductions, or termination may be implemented as described in the Dose Modification section of the Protocol. Part 2 may also explore 1 or more alternate dose regimens that has been investigated in Part 1. Part 2 TGA and TGC will simultaneously enroll at least 5 subjects and up to approximately 10 subjects per treatment group.

Part 3 Dose Expansion

Part 3 of the study will evaluate the dose selected in Part 1 and Part 2 in select tumor types at their respective recommended Phase 2 doses (RP2Ds); based on available data, a dose up to the MTD may be selected as the RP2D for use in each expansion cohort by the sponsor and investigators. There will be three treatment groups in Part 3. Part 3 TGA will enroll up to approximately 155 subjects with specified solid tumors or lymphoma, with a goal of enrolling 5 subjects per tumor type. Part 3 TGB will enroll up to 60 subjects with acute leukemia, MDS, MDS/MPN, or MF. Part 3 TGC will enroll up to approximately 15 subjects with MM. Individual dose modifications (dose interruption, reduction, or termination) will be permitted according to Protocol-defined safety parameters. Subjects will continue to receive INCB054329 in 21-day cycles until withdrawal criteria are met (eg, toxicity, disease progression).

Study Drug, Dosage, and Mode of Administration:

INCB054329 will be administered orally, in tablet form, QD in 21-day cycles. Alternate administration, such as intermediate doses, alternate dosing schedules, or alternate formulations, may be implemented depending upon PK, PD, and safety results.

Reference Therapy, Dosage, and Mode of Administration: Not applicable.

Study Population:

Subjects with advanced malignancies who have failed at least 1 prior therapy or have no standard treatment options demonstrated to provide clinical benefit or who are intolerable to or refuse further standard treatments will be enrolled.

Key Inclusion Criteria:

- Histologically confirmed diagnosis of advanced malignancy that, for Part 3 only, is measurable or evaluable:

  Part 1 Dose Escalation

  - TGA: Any advanced solid tumor or lymphoma (Hodgkin or non-Hodgkin).
  - TGB: Acute leukemia, MDS, MDS/MPN, or MF.

  Part 2 Dose Titration

  - TGA: Any advanced solid tumor or lymphoma.
  - TGC: MM.

  Part 3 Dose Expansion

  - TGA: Diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (with c-MYC translocations), CRC, NSCLC, PanC, CRPC, mBC, ovarian cancer , NMC, other tumor with any pathway alteration relevant to BET protein signaling, such as MYC or SHH pathway activation.
  - TGB: Acute myeloid leukemia (AML), MDS, MDS/MPN (including aCML, CMML, MDS/MPN-U, and RARS T), or MF.
  - TGC: MM, defined as 1 or more of the following:
    - Serum M-protein ≥ 0.5 g/dL.
    - Urine M-protein ≥ 200 mg/24 hours.
    - Serum free light chain (FLC): involved FLC level ≥ 10 mg/dL provided serum FLC ratio is abnormal.
- 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 or refuse the established therapy).
  - MM subjects must have relapsed from or have been refractory to ≥ 2 prior treatment regimens, including proteasome inhibitor and an immunomodulatory drug.
  - AML subjects 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.
  - MF subjects must be resistant, refractory, or intolerant to ruxolitinib therapy.
- Baseline archival tumor specimen available. For solid tumors and lymphoma, a tumor block or 25 unstained slides (15 minimum) from biopsy or resection of primary tumor or metastasis that are ≤ 2 years old (≤ 1 year old and after completion of last treatment is preferred), or willingness to undergo a pretreatment tumor biopsy to obtain the specimen. For acute leukemia, MDS, MDS/MPN, MF, or MM, at least 1 mL archival bone marrow aspirate material ≤ 1 year old and obtained since completion of the prior treatment regimen, or willingness to undergo a pretreatment bone marrow biopsy/aspirate to obtain the specimen. 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.
- Life expectancy > 12 weeks.
- ECOG performance status:
  - Part 1 and Part 2: 0 or 1.
  - Part 3: 0, 1, or 2.

Key Exclusion Criteria:

- Inadequate organ function demonstrated by any of the following:

  Part 1 Dose Escalation

Laboratory Parameter	TGA
Hemoglobin (g/dL)	< 10.0
Platelet count (× 10^9/L)	< 100
Absolute neutrophil count (× 10^9/L)	< 1.5

  Note: No specific hematologic exclusion criteria apply for TGB.

  - Conjugated bilirubin > upper limit of normal (ULN; need only be tested if total bilirubin exceeds > 1.5 × ULN).
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) 1.5 × ULN.
  - Creatinine clearance < 50 mL/min based on Cockroft-Gault formula (< 30 mL/min for MM) or 24-hour urinalysis.

  Part 2 Dose Titration and Part 3 Dose Expansion

Laboratory Parameter	TGA	TGC
Hemoglobin (g/dL)	< 9.0	< 8.0
Platelet count (× 10^9/L)	< 150	< 100
Absolute neutrophil count (× 10^9/L)	< 1.5	< 1.0

  Note: No specific hematologic exclusion criteria apply for TGB in Part 2 and Part 3.

  - Total bilirubin ≥ 1.5 × institutional ULN (total bilirubin > 1.5 × ULN is acceptable if direct bilirubin ≤ 1.2 × ULN or with a diagnosis of Gilbert's syndrome).
  - AST and ALT ≥ 2.5 × ULN or > 5 × ULN for subjects with extensive liver involvement.
  - Creatinine clearance < 40 mL/min based on Cockroft-Gault formula (< 30 mL/min for MM) or 24-hour urinalysis.

- Receipt of anticancer medications, antibodies, biologic, or investigational drugs within the following interval before the first administration of study drug:
  - < 6 weeks for mitomycin-C or nitrosoureas.
  - < 5 half-lives or 14 days, whichever is longer, for any investigational agent (for any indication).
  - < 28 days for any antibodies or biological therapies.
  - < 5 half-lives for all other nonbiologic anticancer medications, or sponsor approval.
  - The following are allowed:
    - Hydroxyurea for controlling proliferative disease and low-dose corticosteroids (prednisone or the equivalent ≤ 10 mg per day).
    - Subjects with CRPC should be maintained on androgen deprivation, chemical or surgical, with a castrate level of testosterone documented (< 50 ng/dL) during the screening period.
    - [redacted]
    - Part 2 TGC and Part 3 TGC: Receipt of less than 160 mg dexamethasone within 14 days before receiving the first dose of study drug.
    - Denosumab and zoledronic acid permitted to treat cancer-related bone diseases such as subjects with prostate or breast cancer.
- Prior receipt of BET inhibitor.
- Type 1 diabetes or uncontrolled Type 2 diabetes.
- HbA1c > 8% (all subjects will have HbA1c test at screening).

- Prior radiotherapy within 2 weeks before first dose of study drug. Palliative radiation treatment to noncentral nervous system, nonindex, or bone lesions performed less than 2 weeks before treatment initiation may be considered with medical monitor approval (a 1-week washout period is usually permitted).
- 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 are eligible. Primary CNS lymphoma will only be permitted in Part 3.
- 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.

Study Schedule/Procedures:

Subjects will have regularly scheduled study visits at the clinical site as part of a 21-day cycle.

Study visits are as follows:

- Screening
- Cycle 1: Day 1, Day 2, Day 8 (± 3 days), Day 15 (± 3 days), Day 16
- Cycles 2 and beyond: Day 1 (± 3 days), Day 11 (± 4 days)
- End of treatment (± 3 days)
- Safety follow-up (end of treatment + 30 days [+ 7 days])
- Survival follow-up (end of treatment + every 9 weeks)

Additionally, Part 1, Cohort 1 TGA will have a visit before the start of the full cycle to receive a single dose of study drug and PK testing (referred to as Day 0). Cycle 1 Day 1 will commence approximately 7 to 10 days later, upon evaluation of the Day 0 PK results.

Local Laboratory Tests:

Most study visits will include sample collection for hematology, chemistry, coagulation, and urinalysis testing to be conducted at a local laboratory. Additionally, the screening visit will include hepatitis testing and fertility/pregnancy testing. Subjects with diseases that are typically monitored through bone marrow examination will have bone marrow biopsy/aspirate at screening and as part of the disease response assessment performed by a local laboratory.

Central Laboratory Tests:

Pharmacodynamic and PK samples will be collected at some visits and shipped to the sponsor or designee for analysis.

Clinical Assessments:

Physical examinations, ECOG performance status, and tumor/disease response assessments will be performed by the investigative site. Electrocardiograms (ECGs) will be performed at the site; data will be submitted to a central reader.

An objective assessment of disease status will be performed at screening, appropriate to the malignancy type (eg, computed tomography [CT], magnetic resonance imaging [MRI], or positron emission tomography [PET]/CT [as applicable by subtype]). Subsequently, disease measurable by CT, MRI, or PET/CT will be assessed approximately every 9 weeks for solid tumors and lymphoma. For disease status assessed in bone marrow, on-treatment biopsies will occur on a limited schedule only if clinically indicated for the subject's diagnosis, if needed to confirm response, or, optionally, to assess PK or PD.

Primary Endpoint:

- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs; through physical examinations; by evaluating changes in vital signs and ECGs; and through clinical laboratory blood and urine sample evaluations.

Secondary Endpoints:

- Pharmacokinetics of INCB054329, including C_{max}, T_{max}, C_{min}, AUC_{0-t}, and Cl/F at Days 1, 2, 8, 15, and 16 of Cycle 1, for subjects in Parts 1, 2, and 3 and any cycle where dose escalation occurs.
- Pharmacodynamic profile of INCB054329 using a whole blood PD assay.
- Evaluation of objective response rate (ORR), progression-free survival (PFS), duration of response (DOR), and overall survival (OS) for subjects in Parts 2 and 3.

[redacted]

Planned Number of Subjects: Part 1: Up to approximately 90 subjects; Part 2: Up to approximately 20; Part 3: Up to approximately 230 subjects (TGA, 155; TGB, 60; and TGC, 15).

Planned Number of Study Sites: Approximately 12 sites.

Principal Coordinating Investigator: TBD

Estimated Duration of Participation:

Up to 28 days for screening, continuous treatment in consecutive 21-day cycles as long as subjects are receiving benefit and have not met any criteria for study withdrawal, and 30 to 37 days for safety follow-up. It is estimated that an individual subject will participate for approximately 4-6 months on average.

Statistical Methods:

Sample size consideration: Part 1 of the study is a standard dose-escalation design, and the sample size depends on the occurrence of safety findings as defined by DLT criteria. Approximately 3 to 6 subjects will be enrolled in each cohort. Part 2 may enroll up to approximately 20 subjects across 2 treatment groups. Part 3 may enroll up to approximately 230 subjects across 3 treatment groups. A cohort of 5 subjects provides a > 80% chance of observing at least 1 responder if the underlying response rate is 30%.

Descriptive statistics (eg, mean, standard deviation, range) will be derived where appropriate. Subject enrollment, disposition, demographics, and medical history will be summarized at baseline. The rate of DLTs will be summarized for each cohort. Dose exposure and intensity will be calculated for each cohort. Safety and disease response data will be compared over time to assess change from baseline. Pharmacokinetic and PD data will be analyzed with appropriate standard nonlinear analytic software.

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LIST OF ABBREVIATIONS

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

Term	Explanation
aCML	atypical chronic myeloid leukemia
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
AR	androgen receptor
AUC	area under the plasma or serum concentration-time curve
BCLU	B-cell lymphoma, unclassifiable
BCRP	breast cancer resistance protein/ABCG2
BD	bromodomain
BET	bromodomain and extra-terminal (protein)
BID	twice daily
BRD	bromodomain-containing protein
BRDT	bromodomain testis-specific protein
CLL	chronic lymphocytic leukemia
CMML	chronic myelomonocytic leukemia
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 remission
CRC	colorectal cancer
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group (performance status assessment)
eCRF	electronic case report form
ELN	European LeukemiaNet

Term	Explanation
EOT	end of treatment
FDA	Food and Drug Administration
FDG	[^{18}F] fluorodeoxyglucose
FISH	fluorescence *in situ* hybridization
FLC	free light chain
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practices
HBV	hepatitis B virus
HBV-DNA	hepatitis B virus deoxyribonucleic acid
HCV	hepatitis C virus
HCV-RNA	hepatitis C virus ribonucleic acid
HIPAA	Health Insurance Portability and Accountability Act of 1996
HNSTD	highest non-severely toxic dose
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IN	Investigator Notification
IRB	Institutional Review Board
IRT	interactive response technology
IWG-MRT	International Working Group–Myeloproliferative Neoplasms Research and Treatment
LDi	longest diameter
mBC	metastatic breast cancer
MDS	myelodysplastic syndrome
MDS/MPN	myelodysplastic/myeloproliferative neoplasms
MDS/MPN-U	myelodysplastic/myeloproliferative neoplasms unclassifiable
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MM	multiple myeloma
MPN	myeloproliferative neoplasms
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells

Term	Explanation
NMC	NUT midline carcinoma
NOAEL	no observed adverse effect level
NSCLC	non–small cell lung cancer
NUT	nuclear protein in testes
OAT	organic anion transporter
OATP1	organic anion transporter polypeptide
OCT2	organic cation transporter
ORR	objective response rate
OS	overall survival
PanC	pancreatic adenocarcinoma
PAD	pharmacologically active dose
PD	pharmacodynamic
PET	positron emission tomography
PFS	progression free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
QD	once daily
QOD	every other day
RARS-T	refractory anemia with ring sideroblasts and thrombocytosis
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SHH	sonic hedgehog (cell pathway)
STD_{10}	severely toxic dose in 10% of animals
SUSAR	suspected unexpected serious adverse reaction
TGA	Treatment Group A
TGB	Treatment Group B
TGC	Treatment Group C
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
WBC	white blood cell

1. INTRODUCTION

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 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 and Esteller 2010). Changes in epigenetic patterns translate to altered transcriptional profiles in malignant cells. In many cases, 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 bromodomain (BD) and extra-terminal (BET) protein family is composed of 4 members (BRD2, BRD3, BRD4, and BRDT) that each have 2 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-containing protein -T is restricted to germ cells; however, BRD2, BRD3, and BRD4 are ubiquitously expressed. Bromodomain and extra-terminal 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 the Mediator co-activator complex, 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. Many of these genes contain "super enhancers" that are notable for binding of BRD4. 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 NUT midline carcinoma (NMC) in which a recurrent translocation of BRD3 or BRD4 with nuclear protein in testes (NUT) creates a novel fusion oncogene, BRD-NUT (French et al 2008). Nuclear protein in testes 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. In particular, c-MYC is upregulated in many cancers secondarily (eg, carcinomas of the breast, colon, cervix, and lung) or directly through chromosomal translocations (eg, some myelomas, double-hit, and Burkitt lymphomas). An example is found with the demonstration that KRAS mutations in non–small cell lung cancer (NSCLC) cells have been shown to maintain c-Myc activation, and treatment with a BET inhibitor induces apoptosis in these cells and promotes tumor regression in murine models (Shimamura et al 2013). In another example, androgen receptor (AR)-dependent prostate cancer cells were highly sensitive to JQ-1 treatment (Wyce et al 2013, Asangani et al 2014), which appeared to be via JQ-1 downregulation of AR activity via BRD4, and resultant inhibition of growth-related target genes. Furthermore, experiments using patient-derived cells from tumors associated with activation of the hedgehog (SHH)-GLI1 pathway, such as in some basal cell carcinomas and medulloblastomas, show that BET inhibition reduces growth and downregulates GLI target genes (Tang et al 2014). These data suggest a therapeutic role for BET inhibitors across a wide range of solid tumor types and demonstrate that cancers derived from aberrant activity of lineage-determining transcription factors may be particularly responsive. For a thorough discussion of preclinical cancer model data, refer to the IB.

Finally targeting BET proteins may have effects beyond direct inhibition 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, for example). 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.

In summary, inhibition of BET protein activity 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. Pharmacology of INCB054329

1.2.1. Biochemical and Cellular Activity

INCB054329 is a selective inhibitor of BET proteins that is proposed for the treatment of advanced cancer. The biochemical potency of INCB054329 to inhibit human BET proteins is determined by an *in vitro* assay that measures binding to a tetra-acetylated human H4 histone derived peptide. Assays for BD1 and BD2 from each of the 4 BET proteins (8 total assays) have been established; potency of INCB054329 ranges from IC_{50} of 1.3 nM to 119 nM among the 8 proteins and is fully reversible (refer to the IB). For BRD4, the protein with the strongest association to cancer, the IC_{50} values for BD1 and BD2 are 28 ± 6.7 nM and 3.0 ± 1.0 nM, respectively.

INCB054329 exhibits inhibitory activity in a wide array of cellular models spanning both hematologic and solid tumor histologies, with an IC_{50} around 200 nM or less in sensitive tumor types. As a comparator, when T-cells from normal donors were stimulated with IL-2 in the presence of INCB054329, an IC_{50} of 1387 ± 242 nM (N = 33) was observed. Among the activities observed are downregulation of BET-controlled genes (such as c-MYC). The c-Myc nuclear transcription factor may be a key downstream target of BET inhibition. Overexpression of c-Myc plays a critical role in malignant transformation, either as a mutant oncogene or by overexpression of the wild-type protein. Overexpression of c-MYC, an important cell-cycle regulator, is observed in many malignancies, including carcinoma of the breast, colon, cervix, and lung, and in myeloid leukemias, among others (Chen et al 2014). The down regulation of c-Myc and other proto-oncogenes may be the mechanism by which BET inhibition reduces cell viability and proliferation in hematologic and solid tumor cell lines, producing cell-cycle arrest and inducing apoptosis (refer to the IB). Together, these data suggest INCB054329 is a strong cellular growth and viability inhibitor, with efficacy across a wide range of histologic tumor types.

1.2.2. Human Whole Blood Assays

To estimate the effect of INCB054329 on c-Myc protein in the presence of human serum proteins, a whole blood assay was developed. INCB054329 treatment reduced c-Myc levels in KMS12BM cells spiked into human whole blood with an IC_{50} value of 92 nM ± 32 (N = 15) and an IC_{90} of 496 nM.

To determine the effect of INCB054329 to suppress production of pro-inflammatory cytokines in human whole blood samples, an assay was developed to measure endogenous levels of MCP-1 and MCP-3 proteins in blood stimulated *ex vivo* with lipopolysaccharide. The IC_{50} values for suppression of MCP-1 and MCP-3 induction are 60 ± 13 and 42 ± 24 nM, respectively, for INCB054329 (n = 4 different donors). These results are consistent with the IC_{50}-value derived from the c-Myc whole blood assay (92 nM). The MCP assay will be used to establish the pharmacodynamic (PD)/pharmacokinetic (PK) relationship in the present study.

1.2.3. *In Vivo* Pharmacology

To evaluate the *in vivo* effect of INCB054329, the RKO xenograft model of colon cancer was established in female Nu/Nu mice. INCB054329 was administered by continuous infusion of 0 (vehicle) 6, 30, or 45 mg/kg per day. Dose-dependent suppression of tumor growth was

observed, with 39%, 59%, and 65% inhibition at 6, 30, and 45 mg/kg per day, respectively. All dose levels were well tolerated. Pharmacokinetic analysis showed that infusions of 30 or 45 mg/kg per day covered the whole blood IC_{90} continuously, whereas 6 mg/kg per day covered the c-Myc whole blood IC_{50}. Therefore efficacy could be achieved when plasma levels of INCB054329 were constantly equivalent to or greater than the c-Myc whole blood IC_{50}.

The effect of different oral dose administration schedules was also evaluated in the MM1.S multiple myeloma (MM) model. Once-daily (QD) and twice-daily schedules were evaluated using oral doses of 0 (vehicle), 25, 50, or 75 mg/kg. Dose-dependent tumor growth inhibition was observed with both schedules (refer to the IB), and a maximum effect of 62% growth inhibition was observed when the c-Myc whole blood IC_{50} was covered for at least 12 hours per day.

To assess the relationship between plasma concentration of INCB054329 and suppression of c-Myc protein in tumors, the KMS12BM multiple myeloma xenograft model was used to enable a direct comparison with c-Myc suppression in the *in vitro* whole blood assay At 3 hours postdose, peripheral blood and tumors were harvested for analysis of drug effect on c-Myc. The *in vivo* observed IC_{50} value of 66 nM for c-Myc suppression by INCB054329 is consistent with the c-Myc *in vitro* whole blood IC_{50} value of 92 nM using KMS12BM-spiked whole blood.

1.3. Preclinical Drug Metabolism and Pharmacokinetics

The absorption, distribution, metabolism, and excretion of INCB054329 have been characterized in rats, dogs, and monkeys (refer to the IB). INCB054329 exhibited species-dependent clearance. In rats, the systemic clearance following intravenous administration was sex-dependent, with approximately 3-fold higher clearance in male rats compared with female rats, and this is attributed to sex-specific hepatic metabolism by CYP3A2 and CYP2C11. The systemic clearance was high in dogs while low in cynomolgus monkeys. The steady-state volume of distribution was moderate while the terminal elimination half-life was short in all 3 species. The renal excretion of intact INCB054329 was minimal across species, suggesting that INCB054329 is eliminated predominantly by metabolism. Following oral administration, INCB054329 exhibited moderate-to-high oral bioavailability in the 3 species. The AUC (see Appendix B) in female rats following oral administration was approximately 10-fold greater than that in male rats, consistent with the differences in systemic clearance and potential differences in presystemic clearance. Based on allometric scaling, the terminal elimination half-life ($t_{½}$) of INCB054329 in human is projected to be approximately 4 hr, and the oral bioavailability is projected to be 50%. At a clinical dose of 50 mg QD, which is expected to cover the whole blood c-Myc IC_{50} (92 nM) over a period of 12 hours, the total steady-state plasma AUC is estimated to be approximately 3.1 μM·h and the C_{max} is estimated to be approximately 0.5 μM.

INCB054329 exhibits moderate *in vitro* permeability using Caco-2 monolayers. INCB054329 has moderate penetration across the rat blood-brain barrier, with steady state brain-to-plasma ratio of 0.35. *In vitro* human serum and plasma protein binding of INCB054329 was moderate (unbound fraction of 24%), similar to that in preclinical species.

Interactions of INCB054329 with uptake and efflux transporters were evaluated using *in vitro* systems. INCB054329 is a weak inhibitor of the 5 uptake transporters (OCT2, OAT3, OATP1B1, OATP1B3 and OAT1) and the 2 efflux transporters (P-glycoprotein [P-gp] and breast cancer resistance protein [BCRP]), and no drug-drug interactions are expected based on

this inhibitory activity. INCB054329 is not a substrate of P-gp but is a substrate of BCRP and therefore, it is possible that the PK profile of INCB054329 is affected by co-administration of potent BCRP inhibitors. INCB054329 is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C19. In contrast to the rat, no sex-dependent differences have been reported for CYP3A4 and CYP2C19 in the human liver. Further, *in vitro* studies conducted using liver microsomes from male and female subjects indicate similar qualitative and quantitative metabolism. Therefore, the PK of INCB054329 is expected to be similar in male and female human subjects. INCB054329 is an inhibitor of CYP2C19 with an IC_{50} value of 9 μM and is not an inhibitor of the other CYPs evaluated. Based on the projected human PK at clinically relevant doses, no drug-drug interaction is expected based on CYP interactions. The metabolism profile of INCB054329 in rat, monkey, and human *in vitro* liver preparations were qualitatively similar and M8 (INCB061050) was identified as the only major metabolite across all 3 species. From the drug safety perspective, no glutathione adducts were detected upon incubation of INCB054329 in human liver microsomes, suggesting that INCB054329 does not generate any reactive metabolites. Metabolites in plasma and urine from the rat and monkey 28-day toxicokinetic studies were similar to those observed *in vitro*.

1.4. Study Rationale

INCB054329 is an oral BET protein inhibitor that is being developed for patients with advanced malignancies. The BET family of BD-containing proteins 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 INCB054329. 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, SHH, and RAS pathways, among others. Preclinical data using INCB054329 as an inhibitor have demonstrated efficacy in these histologic subtypes, such as lymphomas with c-Myc dysfunction, MM, acute myeloid leukemia (AML), castration-resistant prostate cancer (CRPC), colorectal cancer (CRC), pancreatic cancer (PanC), metastatic breast cancer (mBC), and particularly NMC, as discussed previously (refer to the IB). Part 2 of the study will focus on this subset of solid tumors and hematologic malignancies that tend to be associated with these oncogenic profiles, to evaluate the efficacy of BET-inhibition.

1.5. Preclinical Safety and Potential Risks

Non-clinical safety studies with INCB054329 included single and repeat-dose studies of up to 28 days in duration in rats and monkeys using a QD dose schedule. An additional 28-day GLP study was conducted in the rat using an every other day (QoD) dose schedule. The most prominent INCB054329-related findings in toxicology studies conducted in the rat and monkey

were gastrointestinal (GI) toxicity, bone marrow suppression, and lymphoid organ depletion; all of which are expected based on the mechanism of action of INCB054329. Hematology changes associated with the bone marrow suppression and lymphoid depletion included decreases in circulating lymphocytes and platelets. Serum chemistry alterations included increased glucose, as well as increased triglycerides and decreased protein which were likely due to poor nutritional status. The GI toxicity was dose-limiting in the rat, and likely was the main contributor to mortality in this species. Adverse GI toxicity was also noted in the monkey; but was not considered severe at any dose level evaluated. The aforementioned toxicities exhibited evidence of reversibility and are readily clinically monitorable.

Other direct, reversible, dose-dependent toxicities of INCB054329 were identified in the rat only and included ovarian follicular degeneration, hypospermatogenesis, degeneration of the incisor teeth, and histiocytosis of the lung. The changes observed in the reproductive organs are most likely an effect of BRD2 and BRDT inhibition at higher dose levels used in the toxicity studies. Toxicity to teeth is not expected in adult human subjects. INCB054329 was negative in the bacterial mutagenicity assay. *In vivo* carcinogenicity, reproductive and developmental toxicity studies have not been performed. For further detail on nonclinical findings refer to the IB.

1.6. Route, Dose Regimen, and Treatment Period

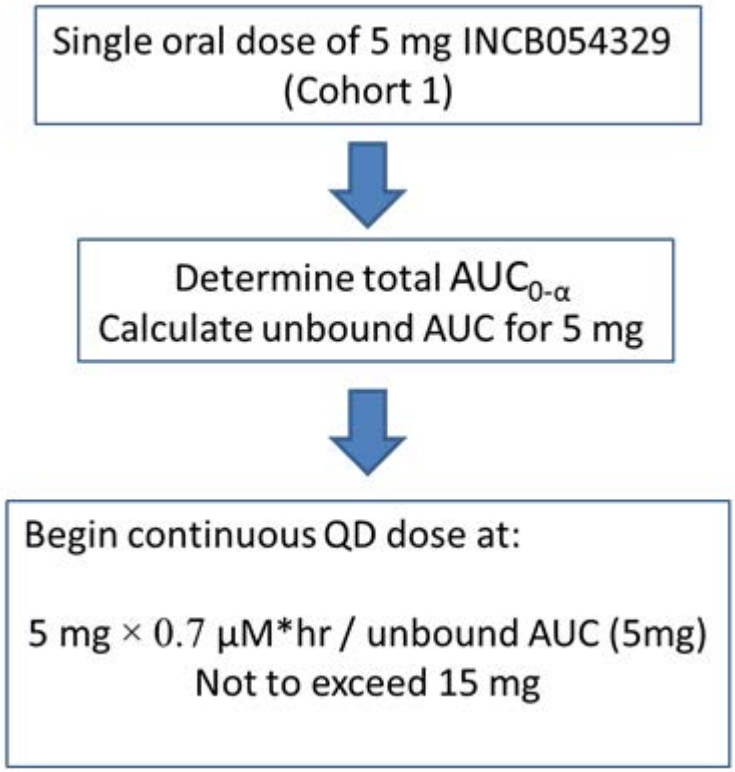
INCB054329 is being developed as a new investigational drug for oral administration. Oral drug administration is generally the most convenient and cost-effective method of drug delivery for medications requiring continuous exposure. INCB054329 tablets will be self-administered QD and will occur in continuous 21-day cycles until discontinuation criteria are met. Alternate dosing schedules, intermediate doses, or alternate formulations may be implemented as PK, PD, and safety data emerge.

According to the algorithms described in ICH S9 Guidance for Industry, Nonclinical Evaluation for Anticancer Pharmaceuticals (FDA 2010), the starting clinical dose for small molecules is often set at one-tenth the STD_{10} in rodents (severely toxic dose in 10% of animals), or one-sixth of the HNSTD (highest non-severely toxic dose) in non-rodents, with the most sensitive species used as a guide. *In vivo* pharmacology studies in mice demonstrated greater efficacy in studies when INCB054329 was administered QD versus QoD. An uninterrupted QD administration regimen is preferred to provide pharmacologic coverage of the target; there are no data to suggest that intermittent inhibition of BET activity would provide an improved therapeutic window. Thus, initiation of Phase 1 clinical investigations using a QD schedule will have the greatest probability of providing a pharmacologically active regimen and potential clinical benefit to study subjects. A dose up to 15 mg is proposed as the safe starting dose for the QD dose regimen, with a dose of 5 mg used for an initial single-dose PK assessment. These dose levels are expected to be safe, based on the following:

- Dose-limiting GI toxicity and bone marrow suppression observed in repeat-dose toxicology studies in both species appear to be reversible and clinically monitorable.
- The proposed initial PK assessment single dose (5 mg) is based on one-tenth of the STD_{10} for the more sensitive species and sex (female rat) and is expected to be safe. This initial single dose will be used to characterize the exposure associated with 5 mg.

- The starting dose for QD dose administration in this study will be determined by the exposure following the single dose with a ceiling of 0.7 µM·h, which is approximately 50% of the unbound AUC observed in male rats at the STD_{10} in the 28-day QD dose study, and the unbound AUC of the male rat NOAEL (no observed adverse effect level) (Figure 1). Calculated doses will be rounded down as needed to available pill strength, or as low as 2.5 mg.
  - Although greater toxicity was observed in female rats given equivalent or lower doses, this was attributed to higher exposure in female rats, and toxicity was similar at comparable exposures. Thus, the exposure associated with male rat STD_{10} may be used to establish an appropriate target exposure for human subjects.
- The starting QD dose will be capped at 15 mg, which is the human equivalent dose for one-tenth of the STD_{10} in male rats in the 28-day QD administration study.
- In monkeys, doses as high as 12 mg/kg per day given QD for 28 days were clinically tolerated (ie, monkeys were less sensitive than rats). The human equivalent dose of 12 mg/kg per day in monkeys is approximately 230 mg/day. This dose (12 mg/kg per day) was associated with an unbound AUC of 6.0 µM·h in males, and 7.8 µM·h in females, which is at least 27-fold higher than the exposure levels predicted for the QD dose (15 mg) in human subjects and approximately 10-fold higher than the ceiling exposure for the starting QD dose.

Figure 1: Determining the Part 1 Treatment Group A Starting Dose



In summary, the toxicity of INCB054329 correlates well with exposure in preclinical studies. Study drug administration in Treatment Group A (TGA) Cohort 1 will begin with an initial PK assessment using a 5 mg single dose. Following the PK assessment, continuous administration will be initiated using a starting dose ranging between 2.5 mg and 15 mg, keeping subjects below the exposure associated with the male rat STD_{10} while minimizing the number of subjects exposed to doses that are unlikely to provide clinical benefit (see Section 4.1.1).

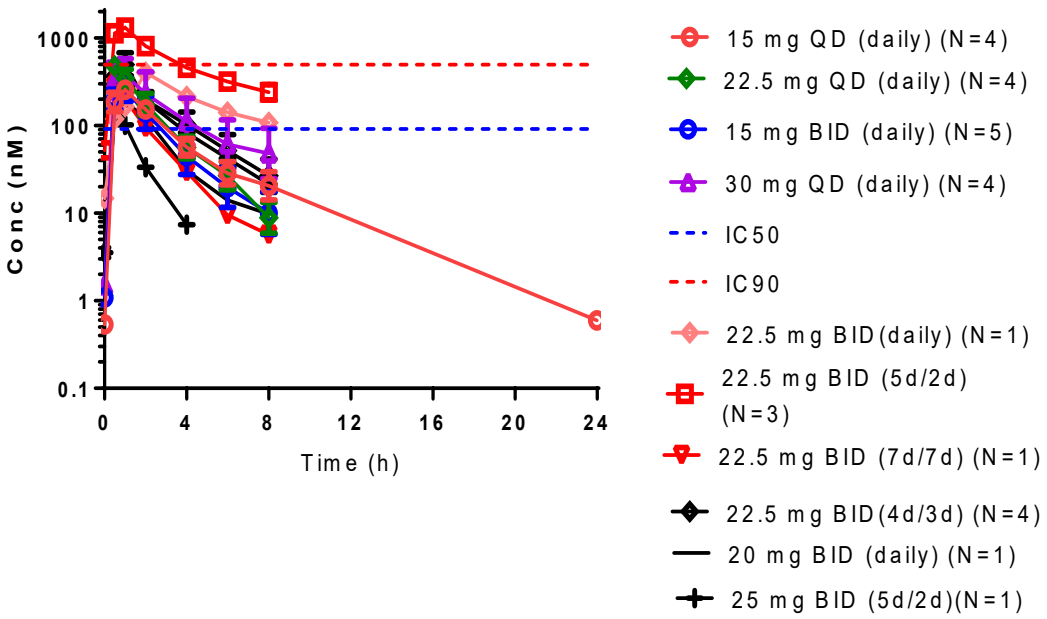
1.7. Clinical Experience With INCB054329 in Study INCB 54329-101

1.7.1. Clinical Pharmacokinetics of INCB054329 in Study INCB 54329-101

The pharmacokinetics of INCB054329 was evaluated following single and multiple doses of 15 mg QD to 25 mg twice daily (BID). Plasma concentrations of INCB054329 decline in a mono-exponential manner with mean terminal elimination half-life of approximately 2 hours with a range of 1.4 to 4.5 hours across cohorts (See Figure 2).

The dosing schema of cohorts is described in Table 1.

Figure 2: INCB054329 Pharmacokinetics at Steady State for Cohorts 1 to 10

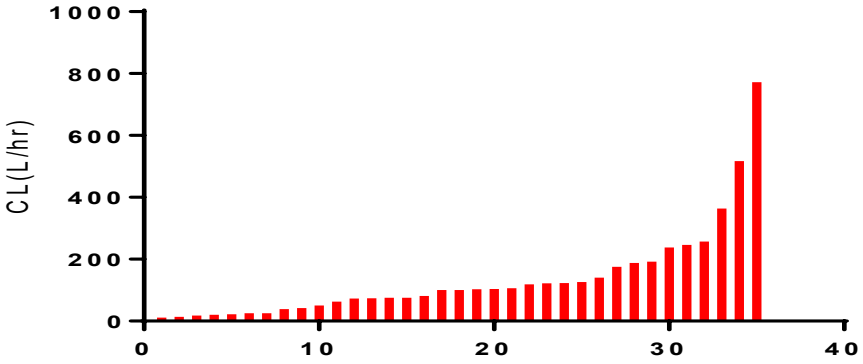


Note: The dose (ie, 15 mg QD) and schedule (ie, daily) were the starting dose and schedule of each cohort. Treatment schedule 5d/2d, 4d/3d, and 7d/7d were study treatments 5 days on/2 days off, 4 days on/3 days off, and 7 days on/7 days off, respectively. The number N refers to the number of subjects in each cohort whose PK data were available for this analysis (see Table 1 for the total number of subjects enrolled in each cohort at the data cutoff).

The pharmacokinetics of INCB054329 is characterized by high intersubject variability, which resulted in overlapping average drug exposure among the cohorts, presumably arising from variability in metabolic clearance. Indeed, metabolic profile of plasma samples indicate high metabolite burden in subjects with low exposure and parent compound and vice versa. The

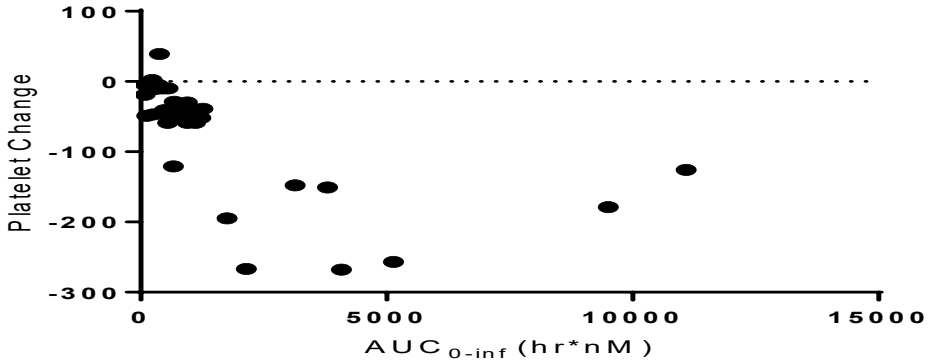
calculated oral clearance of individual subjects is shown in Figure 3, illustrating > 100-fold variability.

Figure 3: INCB054329 Intersubject Variability in Pharmacokinetics Across Cohorts 1 to 10



The exposure-response relationship indicates that the decrease in platelets, which can be considered a pharmacodynamics marker, is well-predicted by AUC (Figure 4), such that exposures higher than ~2000 nM/hour were associated with significant thrombocytopenia (> 100,000/mL drop in platelets). Therefore, for optimal pharmacology and safety, it may be best to titrate each subject to a dose that provides an exposure of ~1500 to ~2000 nM/hour, and this can be achieved by monitoring the change in platelets or other safety parameters within the first 21 days of continuous dose administration, because in most cases, the onset of platelet decreasing and nadir occurred in the first 21 days of treatment.

Figure 4: Maximum Platelet Change From Baseline Versus AUC on Day 1 for Individual Subjects Across Cohorts 1 to 10



Based on the high intersubject variability in pharmacokinetics and the predictable relationship between exposure and platelet change, the protocol was amended to allow intrasubject dose titration (dose escalation or de-escalation) to establish an optimal dose for subjects in Part 2 and Part 3 TGA and TGC of the current protocol (Amendment 2).

1.7.2. Safety and Potential Risks of INCB054329 Based on Preliminary Clinical Experience in Study INCB 54329-101

The first subject was enrolled in the study on 08 JUN 2015. As of 17 OCT 2016, 48 subjects with various advanced solid tumors and lymphomas have been enrolled across 11 cohorts at various dose and schedules (Table 1).

Table 1: Study INCB 54329-101 Part 1 Cohorts

Cohort 1 15 mg QD	Cohort 2 22.5 mg QD	Cohort 3 15 mg BID	Cohort 4 30 mg QD	Cohort 5 22.5 mg BID	Cohort 6 22.5 mg BID 5/2	Cohort 7 22.5 mg BID 4/3	Cohort 8 22.5 mg BID 7/7	Cohort 9 20 mg BID	Cohort 10 25 mg BID 5/2	Cohort 11 25 mg BID 7/7	Total[a]
4	5	6	5	3	4	4	3	7	5	2	48

[a] Treatment schedule 5/2 indicates 5 days on and 2 days off; 4/3 indicates 4 days on and 3 days off; 7/7 indicates 7 days on and 7 days off. The number in the second row indicates the total number of subjects enrolled in each cohort at the data cutoff date, including nonevaluable subjects.

The enrollment started in Part 1 dose escalation with the 3 + 3 design, with a starting dose of 15 mg on a once daily (QD) schedule. Three dose-escalation cohorts using the QD schedule had been completed (Cohort 1, 15mg QD; Cohort 2, 22.5 mg QD; and Cohort 4, 30 mg QD). During the DLT evaluation period (Cycle 1), no DLT was observed in Cohort 1 and 2; 1 DLT (Grade 4 thrombocytopenia) was observed in Cohort 4. Enrollment in Cohort 4 was not expanded beyond the 3 evaluable subjects, due to the fact that the study drug demonstrated a shorter-than-projected half-life ($t_{½}$). The mean terminal phase $t_{½}$ was approximately 2 hours based on PK data from the 3 QD cohorts (Section 1.7.1). Therefore, the decision was made to switch to a twice daily (BID) dose regimen for subsequent cohorts in order to achieve a higher AUC. Two dose-escalation cohorts using the BID continuous daily dosing schedule have been completed (Cohort 3, 15 mg BID, and Cohort 5, 22.5 mg BID). During the DLT evaluation period, no DLT was observed in Cohort 3; 1 DLT (Grade 3 thrombocytopenia with bleeding) was observed in Cohort 5. All 3 subjects in Cohort 5 experienced decreased platelets, 1 with Grade 3 thrombocytopenia with bleeding (DLT), 1 with Grade 4 thrombocytopenia (non-DLT because it occurred on Cycle 2 Day 1, beyond the DLT evaluation period), and 1 with Grade 2 thrombocytopenia. The sponsor and all of the investigators made the decision not to expand Cohort 5 further (ie, not to enroll any additional subjects beyond the 3) due to the observed extent of the overall thrombocytopenia in the cohort.

A decision was also made to explore intermittent dose regimens to decrease the extent of platelet decreasing and/or to allow platelet recovery; the goal is not to totally avoid platelet decreasing, because myelosuppression, mainly thrombocytopenia, is considered an on-target effect of a BET/BRD inhibitor, due to the primary pharmacology of the study drug.

Three cohorts with different intermittent dose regimens were initiated in parallel and have been completed (Cohort 6, 22.5 mg BID 5 days on/2 days off; Cohort 7, 22.5 mg BID 4 days on/3 days off; Cohort 8, 22.5 mg BID 7 days on/7 days off). During the DLT evaluation period, no DLT was observed in these 3 intermittent dose regimen cohorts, and all 3 dose regimens were determined to be tolerated. There were no G3 or G4 thrombocytopenia in these cohorts; however, some subjects did experience various degrees of platelets decreasing. The decision was made to further dose escalate with 2 of the 3 intermittent schedules, 5 days on/2 days off and 7 days on/2 days off. Cohort 10 (25 mg BID 5 days on/2 days off) and Cohort 11 (25 mg BID

7 days on/7 days off) were initiated and enrollments are ongoing. At the data cutoff date, all the slots in Cohorts 10 and 11 have been allocated and in screening.

Examining all the cases of platelet decreasing/thrombocytopenia (all grades and all causality) showed that the majority of them had an onset time around Day 8 and had their large drop in platelet counts between Day 8 and Day 21 during Cycle 1.

Based on available PK data (see Section 1.7.1), a decision was made to investigate the feasibility of intrasubject dose titration in Part 2 Dose Titration (see Section 1.8.1 for rationale). In order to determine the optimal starting dose and schedule for intrasubject dose titration, in parallel to exploring various intermittent dosing schedules as described above, a new cohort with the starting dose of 20 mg BID continuous daily dosing was initiated (Cohort 9). It is hypothesized that a continuous dose regimen may provide better duration of target inhibition and thus better efficacy. No DLT was observed among the first 3 evaluable subjects in Cohort 9; therefore, the starting dose of 20 mg BID is determined to be tolerated. Cohort 9 will enroll a total of 6 evaluable subjects in order to further gather safety and tolerability information with this starting dose to be used in Parts 2 and 3. At the data cutoff date, 7 subjects have been enrolled and 5 were evaluable. Part 1 will stop enrollment once the ongoing cohorts, Cohorts 9, 10 and 11, complete enrollment, and no new cohort will be initiated in Part 1.

As of 17 OCT 2016, 48 subjects received treatment, 43 of them reported at least 1 treatment-emerging adverse event (TEAE; all grades; Table 2). These data were derived from the clinical database and were not cleaned or confirmed; thus, they should be considered preliminary and subject to change. The most frequently reported TEAEs (≥ 20% prevalence) were fatigue, nausea, decreased appetite, constipation, thrombocytopenia, anemia, abdominal pain, and vomiting (Table 2). The most common AEs ≥ Grade 3 (≥ 5% prevalence) were thrombocytopenia, anemia, and fatigue (Table 3). Most cases of thrombocytopenia were considered related to study treatment. Anemia and fatigue were mostly not related to study treatment but rather disease under study. Most adverse events were mild, improved, or resolved with supportive care, and did not require dose interruption or modification. There were 33 SAE events reported; most were considered not related to the study drug. Five SAEs across 3 subjects, thrombocytopenia (4) and anemia (1), were considered related to study treatment by investigators.

Table 2: Summary of TEAEs (≥ 20% Subjects; All Grades, All Causality)

Event	Total[a], % (N = 43)
Fatigue	19 (44.2)
Nausea	18 (41.9)
Decreased appetite	12 (27.9)
Constipation	11 (25.9)
Thrombocytopenia	11 (25.6)
Anemia	10 (23.3)
Abdominal pain	9 (20.9)
Vomiting	9 (20.9)

[a] These data are based on 21 SEP 2016 data extraction, not confirmed, and subject to change.

Table 3: Summary of TEAEs ≥ Grade 3 (≥ 5% Subjects; All Causality)

Adverse Events	Total[a], % (N = 43)
Thrombocytopenia	6 (14.0)
Anemia	5 (11.6)
Fatigue	3 (7.0)

[a] These data are based on 21 SEP 2016 data extraction, not confirmed, and subject to change.

1.8. Rationale for Intrasubject Dose Titration in Part 2

According to the current available PK data (Section 1.7.1), there were larger than expected intersubject variabilities in drug exposure among all the subjects treated with the same starting dose, and this larger variability can be mostly explained by the larger than usual variability in metabolic clearance (Figure 3). This occurred in every dose level/cohort tested so far, resulting in nonlinear and overlapping population PK among different dose levels/cohorts, which make it difficult or almost impossible to evaluable safety and tolerability, MTD, and PAD on a cohort by cohort/dose level by dose level basis. Therefore, it was decided to stop 3 + 3 dose escalation in Part 1 TGA and to not open Part 1 TGC, which is hypothesized to have similar issues as in TGA. Because cytopenia is part of the disease manifestation of subjects in Part 1 TGB (acute leukemia, MDS/MPN, and MF) and thrombocytopenia will not be dose limiting in Part 1 TGB, it is hypothesized that subjects in Part 1 TGB will tolerate doses ≥ 20 mg BID; thus, the 3 + 3 dose escalation in Part 1 TGA will continue to determine PAD/MTD or the safe tolerable RP2D dose. Therefore, TGB will open in Part 1 dose escalation with Amendment 2.

There was a strong correlation between the level of drug exposure and the severity of platelet decrease (Figure 4). The majority of the cases of platelets decreasing occurred during the first cycle. Therefore, the extent of platelet decreasing at the end of the first cycle can be used as a surrogate for drug exposure and as one of the criteria to determine the proper next dose level in the disease types where thrombocytopenia is usually not part of the disease manifestation.

Because myelosuppression, including thrombocytopenia, is based on primary pharmacology/mechanism of action of BRD inhibition, it is hypothesized that the dose would be below optimal if no platelet decreasing is observed at that dose level.

Based on the above, it is reasonable to employ intrasubject dose modulation to evaluate safety and tolerability on an individual basis in order to achieve an optimal drug exposure at which a certain level of platelet decreasing is observed and can be safely and adequately managed. The tolerated level of platelet decreasing will be based on disease type/treatment group, and each treatment group will have different intrasubject dose-escalation criteria (Section 4.1.2.1). Also, timed PK samples will be collected every time dose escalation occurs. Based on correlation between AUC and platelet level change (Figure 4), it is hypothesized that the optimal AUC to be achieved will be approximately 1500 to 2000 nM/hour, and this can be achieved by monitoring the change in platelets or other safety parameters. With intrasubject dose titration, it is possible to achieve an optimal dose and benefit/risk ratio on individual bases to maximize the chance for efficacy.

1.8.1. Part 2 Dose Titration

The starting dose for both TGA and TGC in Part 2 will be the highest tolerated dose with continuous BID dose administration identified in Part 1 TGA; based on available data at the data cutoff date, a starting dose of 20 mg BID continuous dose administration will be used. At the end of Cycle 1, if dose titration criteria are met (Section 4.1.3), the dose may be increased to 25 mg BID on Day 1 of Cycle 2. Dose escalation by no more than 5 mg BID increments may be permitted after each subsequent cycle of treatment if the subject continues to meet the dose titration criteria. Part 2 may also explore 1 or more alternate dose regimens that have been investigated in Part 1 (ie, alternate dose/schedules from Cohorts 6-8 and 10-11) or explore a starting dose < 20 mg BID, if 20 mg BID continuous dosing is considered not optimal pending emerging data.

Dose interruptions, reductions, or termination may be implemented based on toxicity as described in the Protocol (Section 5.6). Treatment will continue until treatment discontinuation criteria or study withdrawal criteria are met (Section 5.6.2 and Section 5.7)

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To evaluate the safety and tolerability of INCB054329 in subjects with advanced malignancies.

2.1.2. Secondary Objectives

- To evaluate the PK and PD of INCB054329 in subjects with advanced malignancies.
- To evaluate preliminary efficacy of INCB054329 in subjects with advanced malignancies.

[redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs; through physical examinations; by evaluating changes in vital signs and ECGs; and through clinical laboratory blood and urine sample evaluations.

2.2.2. Secondary Endpoints

- Pharmacokinetics of INCB054329, including C_{max}, T_{max}, C_{min}, AUC_{0-t}, and Cl/F at Days 1, 2, 8, 15, and 16 of Cycle 1, for subjects in Parts 1, 2 and 3 and any cycle where dose escalation occurs.

- Pharmacodynamic profile of INCB054329 using a whole blood PD assay.
- Evaluation of objective response rate (ORR), progression-free survival (PFS), duration of response (DOR), and overall survival (OS) for subjects in Part 2 and Part 3.

[redacted]

3. SUBJECT ELIGIBILITY

3.1. Study Population

Subjects with advanced malignancies who have failed at least 1 prior therapy or have no standard treatment options demonstrated to provide clinical benefit or who are intolerable to or refuse further standard treatments will be enrolled.

3.1.1. Part 1 Dose Escalation

- Treatment Group A: Any advanced solid tumor or lymphoma.
- Treatment Group B (TGB): Acute leukemia, myelodysplastic syndrome (MDS), myelodysplastic/myeloproliferative neoplasms (MDS/MPN; including atypical chronic myeloid leukemia [aCML], chronic myelomonocytic leukemia [CMML], MDS/MPN unclassifiable [MDS/MPN-U], and refractory anemia with ring sideroblasts and thrombocytosis [RARS-T]), and myelofibrosis (MF).

3.1.2. Part 2 Dose Titration

- TGA: Any advanced solid tumor or lymphoma.
- TGC: MM.

3.1.3. Part 3 Dose Expansion

- TGA: Diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (with c-MYC translocations), CRC, NSCLC, PanC, CRPC, mBC, ovarian cancer, NMC, other tumor with any pathway alteration relevant to BET protein signaling, such as MYC or SHH pathway activation.
- TGB: AML, MDS, MDS/MPN (including aCML, CMML, MDS/MPN-U, and RARS T), or MF.
- TGC: MM.

3.2. Subject Inclusion Criteria

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

1. Men and women aged 18 years or older.
2. Histologically confirmed diagnosis of advanced malignancy that, for Part 3 only, is measurable or evaluable:

   Part 1 Dose Escalation

   a. TGA: Any advanced solid tumor or lymphoma (Hodgkin or non-Hodgkin).
   b. TGB: Acute leukemia, MDS, MDS/MPN, or MF.

   Part 2 Dose Titration

   c. TGA: Any advanced solid tumor or lymphoma.
   d. TGC: MM.

   Part 3 Dose Expansion

   e. TGA: Diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (with c-MYC translocations), CRC, NSCLC, PanC, CRPC, mBC, ovarian cancer, NMC, other tumor with any pathway alteration relevant to BET protein signaling, such as MYC or SHH pathway activation.
   f. TGB: AML, MDS, MDS/MPN (including aCML, CMML, MDS/MPN-U, and RARS T), or MF.
   g. TGC: MM, defined as 1 or more of the following:
      - Serum M-protein ≥ 0.5 g/dL.
      - Urine M-protein ≥ 200 mg/24 hours.
      - Serum free light chain (FLC): involved FLC level ≥ 10 mg/dL provided serum FLC ratio is abnormal.
3. 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 or refuse the established therapy).

   a. MM subjects must have relapsed from or have been refractory to ≥ 2 prior treatment regimens, including proteasome inhibitor and an immunomodulatory drug.
   b. AML subjects 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.
   c. MF subjects must be resistant, refractory, or intolerant to ruxolitinib therapy.
4. Baseline archival tumor specimen available. For solid tumors and lymphoma, a tumor block or 25 unstained slides (15 minimum) from biopsy or resection of primary tumor or metastasis that are ≤ 2 years old (≤ 1 year old and after completion of last treatment is preferred), or willingness to undergo a pretreatment tumor biopsy to obtain the specimen. For acute leukemia, MDS, MDS/MPN, MF, or MM, at least 1 mL archival bone marrow aspirate material ≤ 1 year old and obtained since completion of the prior treatment regimen, or willingness to undergo a pretreatment bone marrow biopsy/aspirate to obtain the specimen. 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.

5. Life expectancy > 12 weeks.
6. ECOG performance status (Appendix C):
   a. Part 1 and Part 2: 0 or 1.
   b. Part 3: 0, 1, or 2.
7. Women of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy, and are not postmenopausal [as defined as ≥ 12 months of amenorrhea]) must have a negative serum pregnancy test at screening and immediately before the first dose of study drug.
8. Men and women of childbearing potential must agree to take appropriate precautions to avoid pregnancy or fathering children (with at least 99% certainty) from screening through follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
9. Ability to comprehend and willingness to sign an Informed Consent Form (ICF).

3.3. Subject Exclusion Criteria

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

1. Inadequate organ function demonstrated by any of the following:

   Part 1 Dose Escalation

	Laboratory Parameter	TGA
a.	Hemoglobin (g/dL)	< 10.0
b.	Platelet count (× 10^9/L)	< 100
c.	Absolute neutrophil count (× 10^9/L)	< 1.5

Note: No specific hematologic exclusion criteria applicable for TGB.

   d. Conjugated bilirubin > upper limit of normal (ULN; need only be tested if total bilirubin exceeds > 1.5 × ULN).
   e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) 1.2 × ULN.
   f. Creatinine clearance < 50 mL/min based on Cockroft-Gault formula (< 30 mL/min for MM) or 24-hour urinalysis.

   Part 2 Dose Titration and Part 3 Dose Expansion

	Laboratory Parameter	TGA	TGC
g.	Hemoglobin (g/dL)	< 9.0	< 8.0
h.	Platelet count (× 10^9/L)	< 150	< 100
i.	Absolute neutrophil count (× 10^9/L)	< 1.5	< 1.0

Note: No specific hematologic exclusion criteria apply for TGB in Part 2 and Part 3.

   j. Total bilirubin ≥ 1.5 × institutional ULN (total bilirubin > 1.5 × ULN is acceptable if direct bilirubin ≤ 1.2 × ULN or with a diagnosis of Gilbert's syndrome).

k. AST and ALT ≥ 2.5 × ULN, or > 5 × ULN for subjects with extensive liver involvement.
l. Creatinine clearance < 40 mL/min based on Cockroft-Gault formula (< 30 mL/min for MM) or 24-hour urinalysis.

2. Receipt of anticancer medications, antibodies, biologic, or investigational drugs within the following interval before the first administration of study drug:
   a. < 6 weeks for mitomycin-C or nitrosoureas.
   b. < 5 half-lives or 14 days, whichever is longer, for any investigational agent (for any indication).
   c. < 28 days for any antibodies or biological therapies.
   d. < 5 half-lives for all other nonbiologic, anticancer medications, or sponsor approval.
   e. The following are allowed:
      – Hydroxyurea for controlling proliferative disease and low-dose corticosteroids (prednisone or the equivalent ≤ 10 mg per day).
      – Subjects with CRPC should be maintained on androgen deprivation, chemical or surgical, with a castrate level of testosterone documented (< 50 ng/dL) during the screening period.
      – [redacted]
      – Part 2 TGC and Part 3 TGC: Receipt of less than 160 mg dexamethasone within 14 days before receiving the first dose of study drug.
      – Denosumab and zoledronic acid permitted to treat cancer-related bone diseases such as subjects with prostate or breast cancer.

3. 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 (including, but not limited to, cyclosporine, tacrolimus, mycophenolate mofetil, or corticosteroids [in excess of 10 mg prednisone equivalent per day]) following allogeneic transplant within 2 weeks of Cycle 1 Day 1.
4. Unless approved by the medical monitor, may not have received autologous hematopoietic stem cell transplant within 3 months before treatment.
5. Prior receipt of any BET inhibitor.
6. Type 1 diabetes or uncontrolled Type 2 diabetes
7. HbA1c of > 8% (all subjects will have HbA1c test at screening).
8. Prior radiotherapy within 2 weeks before first dose of study drug. Palliative radiation treatment to noncentral nervous system, nonindex, or bone lesions performed less than 2 weeks before treatment initiation may be considered with medical monitor approval (a 1-week washout period is usually permitted).
9. Known human immunodeficiency virus infection.

10. Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as defined in Section 7.4.6.2.
11. Chronic or current active uncontrolled infectious disease requiring systemic antibiotic, antifungal, or antiviral treatment.
12. Untreated brain or CNS metastases or brain/CNS metastases that have progressed (eg, evidence of new or enlarging brain metastasis or new neurological symptoms attributable to brain/CNS metastases). Subjects with previously treated and clinically stable brain/CNS metastases and off all corticosteroids for ≥ 2 weeks are eligible. Primary CNS lymphoma will only be permitted in Part 3.
13. History or presence of abnormal electrocardiogram (ECG) which, in the investigator's opinion, is clinically meaningful. A screening QTc interval of > 470 milliseconds 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.
14. History of clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction (MI), New York Heart Association (NYHA) Class III or IV congestive heart failure, or clinically significant arrhythmias not controlled by medication. Subjects with a pacemaker and well-controlled rhythm for at least 1 month before first dose of study medication will be allowed.
15. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or *in situ* cervical cancer that has undergone potentially curative therapy.
16. History of allergic reactions to INCB054329, similar compounds, or the excipients of INCB054329.
17. Unable or unwilling to swallow INCB054329 or significant GI disorder that could interfere with the absorption, metabolism, or excretion.
18. Subjects unwilling to be transfused with blood components.
19. Current condition requiring the use of a prohibited concomitant medication (see Section 5.10).
20. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
21. Women who are pregnant or nursing.
22. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits, pose a significant risk to the subject, or interfere with interpretation of study data.
23. Any unresolved toxicity ≥ Grade 2 from previous anticancer therapy except for stable chronic toxicities (≤ Grade 2) not expected to resolve, such as stable Grade 2 peripheral neuropathy.
24. Any sign of clinically significant bleeding.

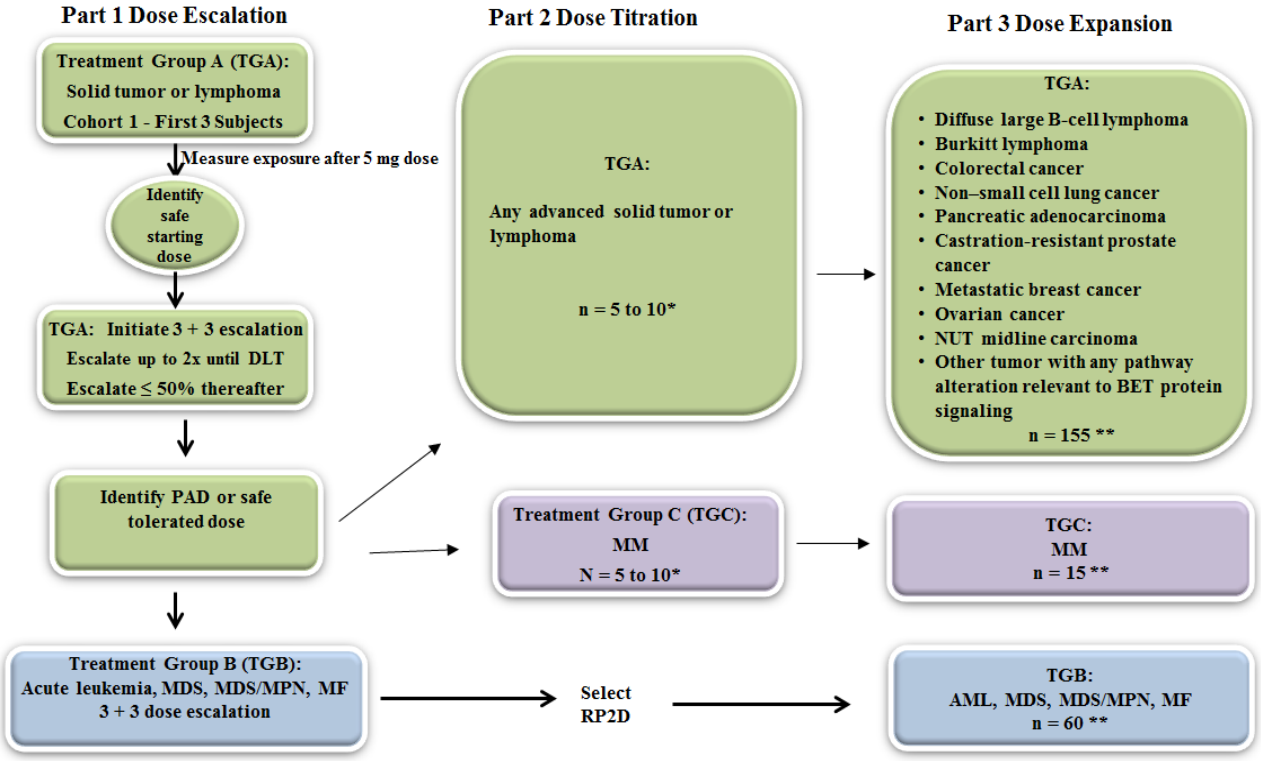
4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label, dose-escalation study of INCB054329 in subjects with advanced malignancies. Subjects will receive QD doses of INCB054329 continuously in 21-day cycles. Alternative schedules may be assessed if indicated by safety, PK, or PD data. The study will be conducted in 3 parts (See Figure 5).

- Part 1 Dose Escalation will determine the maximum tolerated dose (MTD) of INCB054329 and/or a tolerated dose that reaches the desired target inhibition (ie, a pharmacologically active dose [PAD]).
- Part 2 Dose Titration will determine the feasibility of intrasubject dose titration using Protocol-defined criteria.
- Part 3 Dose Expansion will evaluate the doses and schedules selected in Part 1 and Part 2 in subjects with select tumor types postulated to be particularly susceptible to BET inhibition (see inclusion criteria, Section 3.2).

Figure 5: Study Design



*Part 2 Dose Titration: TGA and TGC will enroll simultaneously at least 5 subjects and up to approximately 10 subjects per treatment group titrating each subject per Protocol-defined dose titration criteria.

** Part 3 Dose Expansion: TGA, TGB, and TGC, will enroll up to 5 subjects per tumor type in each treatment group, with the exception of 'TGA: Other tumor with c-MYC or SHH pathway activation which is considered an assorted basket and may enroll up to 15 subjects.' If ≥ 1 out of 5 of the select tumor types demonstrates clinically meaningful benefit, enrollment in that select tumor type will then continue to enroll up to approximately 15 subjects with that tumor type. If activity is not demonstrated, no further subjects will be dosed within that particular tumor type.

4.1.1. Part 1 Dose Escalation

The study will begin with open-label dose escalation in TGA, using a 3 + 3 design to determine the tolerated dose over a 21-day cycle. Initially, subjects in Cohort 1 will receive a single dose of INCB054329 followed by a timed PK assessment to confirm exposure approximately 1 week before continuous administration is initiated (referred to as Day 0). The starting dose for continuous administration will be determined based on the exposures assessed at this PK assessment; this dose will be no higher than 15 mg.

The dose-escalation portion of the study will be conducted in the following treatment groups:

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

Escalation will begin with Cohort 1 (including the Day 0 single-dose PK assessment) in TGA.

The Day 0 PK assessment will be used to establish exposure for the initial dose of 5 mg. This exposure will determine the starting dose for the subject on Day 1, according to the formula described in Section 1.6. It is anticipated that this will result in a 15 mg QD starting dose. In the event that the 5 mg exposure projects a safe starting dose lower than 15 mg for a given subject, this subject will receive the calculated safe starting dose rounded down to the closest tablet strength. Subsequent subjects in Cohort 1 will not receive a higher starting dose than any previous subject. Thus subjects will have a starting dose chosen to produce a projected unbound exposure of ≤ 0.7 μM·h (based upon the subject with the highest exposure). Previously enrolled subjects may continue at the dose at which they began on Day 1, because this dose has already been confirmed to result in an acceptable exposure in that subject. The safety data (eg, dose-limiting toxicities [DLTs]) from all subjects in Cohort 1 will be evaluated as a group for purposes of establishing the safety for the dose level within the 3 + 3 design. The dose level for the cohort will be considered to be that of the subject receiving the lowest starting dose in Cohort 1.

Treatment Group B will begin enrollment at the PAD (plasma concentration exceeding the PK which is projected to inhibit c-Myc level $\geq 50\%$ for approximately 10 hours) or a tolerated dose identified in TGA at the discretion of the sponsor, and dose escalation will proceed independently to an MTD in each treatment group using a 3 + 3 design. Treatment Group C will open in Part 2 instead of Part 1 (see rationale in Section 1.8). Alternative dose regimen(s) may be explored, such as BID or intermittent dose regimens, pending emerging PK, PD, and safety data. 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, the next cohort will begin enrollment at the next highest dose level. Subjects not receiving at least 80% of the planned study drug doses during the first cycle (ie, $\geq$ 17 of 21 doses during QD dosing or 34 of the 42 BID doses in Cycle 1) will be considered nonevaluable for purposes of determining the MTD (unless due to a DLT) and will be replaced. Cohorts may include an additional subject to ensure that enough evaluable subjects reach Day 21.

Dose increases between cohorts may be up to 2-fold until a Grade 2 toxicity is observed, after which dose increases will be limited to no more than 50% above the previous level. Exceptions are toxicities with a clear alternative explanation or transient abnormal laboratory values without clinically significant signs or symptoms. If 1 DLT (see Section 5.4) is observed in the first 3 subjects in a cohort, 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 that at which one-third or more of subjects in a particular cohort report DLTs. If the Cohort 1 dose is not tolerated (≥ 2 of 6 subjects report a DLT), dose de-escalation will be considered in order to identify a tolerated dose. The next tested dose will be reduced by at least 25% (depending upon emerging PK and safety data). Up to 4 total de-escalations may be explored if plasma concentrations are within pharmacologically active range.

If a PAD (plasma concentration expected to inhibit c-Myc level ≥ 50% for approximately 10 hours) is reached before identifying the MTD, the PAD may be selected for use in the expansion cohort (Part 3), at the discretion of the sponsor. In the event that unique toxicities are observed relative to tumor type, the sponsor may elect to explore a split dose escalation to identify a category-specific MTD or PAD (eg, if the data suggest a different tolerability for lymphoid malignancies vs solid tumors). The sponsor may implement alternate administration schedules or alternate formulations depending on PK, PD, and safety results. Individual subjects within each cohort will undergo reductions/interruptions in INCB054329 administration according to prescribed safety parameters.

4.1.2. Part 2 Dose Titration

Due to emerging PK and PD data from the ongoing INCB 54329-101 study Part 1 TGA (Sections 1.7.1 and 1.7.2; larger than expected intersubject variability in drug exposure), Part 2 will enroll 2 treatment groups to investigate the feasibility of intrasubject dose titration with Protocol-defined criteria (Section 4.1.2.1). Part 2 TGA will enroll advanced solid tumors and lymphomas; Part 2 TGC will enroll multiple myeloma (MM). The starting dose will be the highest tolerated dose with continuous BID dose administration identified in Part 1 TGA. At the data cutoff date, the highest tolerated dose with continuous dose administration identified in Part 1 TGA was 20 mg BID, which will be used as the starting dose for Part 2 TGA and TGC; an alternative starting dose may be chosen pending emerging data. Part 2 TGA and TGC will simultaneously enroll at least 5 subjects and up to approximately 10 subjects per treatment group. At the end of Cycle 1, if dose titration criteria are met (Section 4.1.2.1), the dose may be increased to 25 mg BID on Day 1 of Cycle 2. Dose escalation by ≤ 5 mg BID increments may be permitted after each subsequent cycle of treatment if the subject continues to meet the dose-escalation criteria. Dose interruptions, reductions, or termination may be implemented as described in Section 5.6, Dose Modifications. Once a treatment group is completed in Part 2, that individual treatment group may move into Part 3 without the other treatment group being completed in Part 2. Part 2 may also explore 1 or more alternate dose regimens that has been investigated in Part 1 or may explore a starting dose of < 20 mg BID, if 20 mg BID dose administration is considered not optimal pending emerging data from Part 2.

4.1.2.1. Dose Titration Criteria

Subjects must meet all the following criteria for dose escalation, including the ones applicable to all treatment groups (TGA/TGC) and the ones specific to each treatment group as outlined in the following:

Dose titration applicable to TGA/TGC:

- The subject must have received treatment for at least one 21-day cycle or at least 80% of the prescribed doses (34 of the 42 BID doses or ≥ 17 of the 21 days of treatment) during the dose-escalation evaluation period.
- Each dose escalation is limited to ≤ 5 mg BID.
- The Protocol eligibility criteria are met at the time of dose escalation.
- The subject does not meet any DLT criteria (Section 5.5).
- The subject does not meet any treatment discontinuation criteria (Section 5.7).
- The subject is willing to submit to the key PK and safety assessments as required in Cycle 1, including PK, ECGs, safety laboratory assessments, targeted physical examinations, and vital signs.
- In the opinion of the investigator, the subject does not have any concurrent condition or circumstance that would complicate the dose escalation or PK sampling or would pose increased risk to the subject.

Dose titration applicable to TGA only:

- Platelet level change from the baseline or the previous dose-escalation decision is ≤ 30% drop AND the NADIR during the evaluation period is $>100 \times 10^9$/L.

Dose titration applicable to TGC only:

- Platelet level change from the baseline or the previous dose escalation decision is ≤ 30% drop AND the NADIR during the evaluation period $> 75 \times 10^9$/L.

4.1.3. Part 3 Dose Expansion

Part 3 of the study will evaluate the dose selected in Part 1 and Part 2 in select tumor types at their respective recommended Phase 2 doses (RP2Ds); based on available data, a dose up to the MTD may be selected as the RP2D for use in each expansion cohort by the sponsor and investigators.

Part 3 TGA will enroll up to approximately 135 subjects with specified solid tumors or lymphoma, with a goal of enrolling 5 subjects per tumor type. If ≥ 1 out of 5 of the select tumor types demonstrates clinically meaningful benefit, enrollment in that select tumor type will then continue to enroll up to approximately 15 subjects with that tumor type. If activity is not demonstrated, no further subjects will be treated within that particular tumor type. Tumor types are as follows: DLBCL, Burkitt lymphoma, CRC, NSCLC, PanC, CRPC, mBC, ovarian cancer, and NMC. An additional group of up to approximately 20 subjects with any tumor known to have c-MYC or SHH pathway activation will also be enrolled, of whom no less than 5 will have DLBCL with a known aberration of MYC and BCL2 and/or BCL6 (ie, "double-hit" DLBCL) or

B-cell lymphoma, unclassifiable (BCLU) with features intermediate between DLBCL and Burkitt lymphoma. This totals approximately 155 subjects for Part 3 TGA.

Part 3 TGB will enroll up to 60 subjects with AML, MDS, MDS/MPN, or MF.

Part 3 TGC will enroll up to approximately 15 subjects with measureable/evaluable MM.

Individual dose modifications (dose interruption, reduction, or termination) will be permitted according to Protocol-defined safety parameters. Subjects will continue to receive INCB054329 in 21-day cycles until withdrawal criteria are met (eg, toxicity, disease progression). Part 3 TGA (solid tumors and lymphoma) will also include a food-effect study for the first 12 subjects enrolled.

4.2. Measures Taken to Avoid Bias

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

4.3. Number of Subjects

Part 1: Up to approximately 90 subjects; Part 2: Up to approximately 20; Part 3: Up to approximately 230 subjects (TGA, 155; TGB, 60; and TGC, 15).

4.4. 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 IRB/IEC in writing of the study's completion or early termination, and send a copy of the notification to the sponsor or sponsor's designee and retain 1 copy for the site study regulatory file.

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

5. TREATMENT

5.1. Treatment Groups and Administration of Study Drug

In this study, subjects will be enrolled into Part 1, Part 2, Part 3 as described previously, with all subjects receiving INCB054329 (ie, the study drug). Subjects will self-administer study drug at home, except on days when PK is assessed, using an oral QD/BID regimen that will vary by cohort, and will be prescribed and managed by the study investigator. One cycle will be defined as 21 continuous days of planned study treatment; subjects will receive treatment in continuous cycles unless interrupted for safety reasons.

5.1.1. Study Drug

INCB054329 drug product is formulated as immediate release (IR) tablets in strengths of 2.5 mg and 15 mg. The tablets of both strengths are round and white to off-white in color and contain the active drug substance along with the excipients microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. Study drug tablets are packaged in high-density polyethylene (HDPE) bottles; no preparation is required. Bottles should be stored at room temperature, 15°C to 30°C (59°F to 86°F) and closed tightly to protect the tablets from humidity. See Section 10.2 for details regarding the accountability, handling, and disposal of study drug. All Incyte investigational product will be labeled with the following statement, "Caution: New Drug—Limited by the United States law to investigational use," or in accordance with local regulatory requirements as applicable.

5.1.2. Administration Instructions and Treatment Compliance

Subjects should be counseled by the investigator to maintain strict adherence to the study regimen as prescribed, and to keep a record of any missed doses. The subject will be instructed to bring all unopened, empty, and opened/partially used bottles of study drug to each study visit, at which time compliance will be assessed (see Section 7.8.2).

5.2. Randomization and Blinding

Not applicable.

5.3. Duration of Treatment and Subject Participation

Up to 28 days for screening, continuous treatment in consecutive 21-day cycles as long as subjects are receiving benefit and have not met any criteria for study withdrawal, and 30 to 37 days for safety follow-up. It is estimated that an individual subject will participate for approximately 4 to 6 months on average (see Withdrawal Criteria, Section 5.7.1).

5.4. Treatment Compliance

Treatment compliance with all study-related medications and procedures should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with INCB054329 will be calculated, by the sponsor, based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Instructions for subjects and details for assessing compliance are provided in Section 7.8.2).

5.5. Dose-Limiting Toxicity and Maximum Tolerated Dose

Dose-limiting toxicity will be defined as any of the toxicities in Table 4 occurring up to and including Day 21 in subjects enrolled in Part 1. In Part 2 and Part 3, DLTs will also be evaluated as part of the dose-titration criterion. The DLTs include all AEs of the specified grades, regardless of investigator assessment of causality to the investigational product. Only AEs with a clear alternative explanation (eg, due to disease progression) or transient laboratory values without associated clinically significant signs or symptoms (as determined by the investigator) can be deemed non-DLT.

Individual subject dose reductions may be made based on events observed at any time during treatment with INCB054329; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD, decisions will be made based on events that are observed from the Cycle 1 Day 1 through and including the final day of Cycle 1 (Day 21). A lower MTD may subsequently be determined based on relevant toxicities that become evident after Day 21. All DLTs will be assessed by the investigator using the current CTCAE v4.03 criteria (NCI 2010).

Table 4: Definition of Dose-Limiting Toxicity and Maximum Tolerated Dose

DLTs Include the Following
Nonhematologic DLTs
• Any ≥ Grade 3 nonhematologic toxicity EXCEPT: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. – Asymptomatic changes in fasting cholesterol and triglycerides. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. – Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions).
Hematologic DLTs (TGA and TGC Only)
• Grade 3 thrombocytopenia with bleeding requiring transfusion of packed red blood cells. • Grade 4 thrombocytopenia. • Febrile neutropenia (absolute neutrophil count < 1.0×10^9/L and fever > 101°F/38.5°C). • Grade 4 neutropenia that does not recover to ≤ Grade 2 in ≤ 7 days after interrupting study drug. • Grade 4 anemia. (Hematology results may be repeated once within 72 hours to confirm the result).
Hematologic DLTs (TGB Only)
• Grade 4 thrombocytopenia persisting for more than 6 weeks after initiation of treatment in subjects whose bone marrow assessment showed less than 5% blasts and no significant dysplasia. • Grade 4 neutropenia persistent for more than 6 weeks after initiation of treatment in subjects whose bone marrow assessment showed less than 5% blasts and no significant dysplasia. • Given the high frequency of prevalence of disease-related cytopenias and infectious complications for subjects in TGB, especially in AML and high-risk MDS population, events related to underlying disease, including but not limited to bleeding, infection, and febrile neutropenia, are not considered DLTs unless severity or duration is longer than that expected with standard-of-care treatment.
MTD
• MTD will be defined as 1 dose level below that at which ≥ one-third of subjects in a particular cohort report DLTs. Dose-limiting toxicity will be defined as the any of the toxicities in this table occurring up to and including study Day 21 for Cycle 1 and any cycle where dose escalation occurs.

Dose-limiting toxicities will be followed until resolved to baseline or until stabilized for a minimum of 4 weeks. During follow-up, subjects should be seen as often as medically indicated to assure safety. In all cases, investigators are free to employ any measures or concomitant medications, following discussion with the sponsor (whenever possible), necessary to optimally treat the subject.

5.6. Dose Modifications

Subjects will be assigned a starting dose based upon the cohort in which they are enrolled. Dose reductions for safety, restarts, or increases are to follow the guidance in this section.

5.6.1. Interruption and Restarting of Study Drug

Treatment with INCB054329 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 INCB054329.

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

Table 5: Guidelines for Interruption and Restarting of Study Drug

CHEMISTRY	
Adverse Event	**Action Taken**
• AST and/or ALT is > 3.0 × ULN AND < 5.0 × ULN for > 7days, OR • AST and/or ALT is > 5.0 AND < 20 × ULN. Note: In subjects with liver metastasis-related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.	1. Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except by approval of the medical monitor. 2. Restart study drug at same dose. Monitor as clinically indicated. NB: If criteria for dose interruption met again, upon restart of study drug, repeat Step 1, and restart study drug at next lower dose (or at 25% reduction, rounded down to the nearest strength).
• 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.	1. Discontinue study drug.

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

HEMATOLOGY			
Parameter	**Treatment Group/ Expansion Cohort**	**Adverse Event**	**Action Taken**
Platelet count ($\times 10^9$/L)	Part 1 TGA	50 to < 75	1. Hold until resolved to ≥ 75. 2. Restart study drug at same dose and monitor.
		< 50	1. Hold until resolved to ≥ 75. 2. If recovery to ≥ 75 in ≤ 7 days, restart study drug at same dose and monitor. If recovery to ≥ 75 in > 7 days, restart study drug at next lower dose and monitor.
	Part 2 and Part 3 TGA and TGC	25 to < 50	1. Hold until resolved to ≥ 50. 2. Restart study drug at same dose and monitor.
		< 25	1. Hold until resolved to ≥ 50. 2. If recovery to ≥ 50 in ≤ 7 days, restart study drug at same dose and monitor. If recovery to ≥ 50 in > 7 days, restart study drug at next lower dose and monitor.
	Part 1 and Part 3 TGB		Manage as per institutional standard relevant to the underlying disease. Consult with the medical monitor for management outside of the institutional standard.
Absolute neutrophil count ($\times 10^9$/L)	Part 1 TGA	< 1.0	1. Hold until resolved to ≥ 1.0. 2. If recovery to ≥ 1.0 in ≤ 7 days, restart study drug at same dose and monitor. If recovery to ≥ 1.0 in > 7 days, restart study drug at next lower dose and monitor.
	Part 2 and Part 3 TGA and TGC	< 0.5	1. Hold until resolved to ≥ 0.5. 2. If recovery to ≥ 0.5 in ≤ 7 days, restart study drug at same dose and monitor. If recovery to ≥ 0.5 in > 7 days, restart study drug at next lower dose and monitor.
	Part 1 and Part 3 TGB		Manage as per institutional standard relevant to the underlying disease. Consult with the medical monitor for management outside of the institutional standard.
Hemoglobin ($\times 10^9$/L)	All parts TGA and TGC	< 8.0	1. Hold until resolved to ≥ 10.0; monitor CBC approximately every 3 days. 2. Restart at next lower dose and monitor per Protocol.
		< 6.5	Discontinue study treatment.
	Part 1 and Part 3 TGB		Manage as per institutional standard relevant to the underlying disease. Consult with the medical monitor for management outside of the institutional standard.
OTHER TOXICITIES			
Adverse Event			Action Taken
• Any Grade 1 or Grade 2 toxicity.			Continue study drug treatment and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care.			1. Interrupt study drug up to 2 weeks (14 days), until toxicity resolves to ≤ Grade 1. 2. Restart study drug at same dose. If assessed as related to study drug, restart study drug 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 study drug administration and follow-up per Protocol. (Exceptions require approval of sponsor.)
• Any other Grade 4 toxicity.			Discontinue study drug administration and follow-up per Protocol.

5.6.2. Criteria for Permanent Discontinuation of Study Drug

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

- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- An AE requiring more than 2 dose reductions, if below the PAD of INCB054329.
- Persistent AE requiring a delay of therapy for more than 2 weeks (14 days) unless a greater delay has been approved by the sponsor.

5.6.3. Dose Increases

For Parts 1 and 3 TGB, intrasubject dose escalation will be permitted with sponsor preapproval in the following circumstances:

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

For Parts 2 and 3, TGA and TGC, intrasubject dose escalation will follow the dose titration criteria (Section 4.1.2.1).

5.7. Withdrawal of Subjects From the Study

5.7.1. Withdrawal Criteria

Subjects **must** be withdrawn from treatment with INCB054329 for the following reasons:

- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The subject becomes pregnant.
- Consent is withdrawn.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB/IEC.
- Occurrence of an AE defined as unacceptable toxicity (see Section 5.6.2).

- Any AE (even if unrelated to treatment) requiring more than a 2-week delay in study drug, unless approved by the sponsor.
- Disease progression has occurred.

A subject **may** be withdrawn 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 opinion of the investigator, the sponsor should be consulted to determine whether to withdraw the subject from study treatment.

5.7.2. Withdrawal Procedures

When the decision is made to permanently discontinue the study drug (EOT) the treatment phase will be considered complete.

If a subject is withdrawn from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal and the last dose of study drug must be documented in the subject's medical record and in the electronic case report form (eCRF).
- The EOT visit should be performed (see Section 6.4).
- Reasonable efforts should be made to have the subject return for the safety follow-up visit (see Section 6.5.1), and survival follow-up (see Section 6.5.2) will begin.
- Regardless of the occurrence of the safety follow-up visit (scheduled for 30 to37 days after the last dose of study drug), the obligatory follow-up period is 30 days after the last dose of study drug was received. Subjects must be followed for safety until any study drug-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

5.8. Concomitant Medications and Measures

There are no mandatory concomitant medications or measures. The investigator will provide care for the subject's medical condition according to institutional standards. All concomitant medications and treatments or procedures conducted from 30 days before the first dose of study drug, through 30 days after the last dose of study drug are considered concomitant, and must be recorded in the eCRF.

5.9. Restricted Medications and Measures

Chronic glucocorticoid administration is discouraged; if required for medical management doses should not exceed 10 mg/day prednisone (or equivalent). Acute administration of glucocorticoids for any indication should be recorded promptly in the eCRF.

Short courses of systemic corticosteroid doses ≤ 10 mg/day prednisone (or equivalent) are permitted (eg, for transfusion reaction prophylaxis) but discouraged from the screening visit through the EOT visit or last dose of study medication.

The following require sponsor approval:

- Hydroxyurea for controlling proliferative disease is permitted with medical monitor approval.
- Because of the potential to influence the plasma concentration of the study drug (Suzuki et al 2009), the proton pump inhibitors (PPIs) omeprazole and lansoprazole are permitted only with sponsor approval and other PPIs are prohibited (Section 5.10). Additionally, inhibitors or inducers of CYP2C19 (Appendix E), and moderate or weak inducers and inhibitors of CYP3A4 require sponsor approval; note that these include ticlopidine, clopidogrel, and oral contraceptives.
- 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 CYP2C19 or CYP3A4, or of PPIs, during the study.

These medications should be taken regularly rather than as needed.

5.10. Prohibited Medications and Measures

- Any anticancer medication other than the study drug. Denosumab and zoledronic acid are permitted to treat cancer related bone diseases such as subject with prostate and breast cancer.
- Any investigational study drug, for any indication.
- Potent inhibitors or inducers of CYP3A4 (Appendix D) with the exception of topical ketoconazole, based on its low overall bioavailability.
- BCRP (Breast Cancer Resistance Protein/ABCG2) inhibitors, specifically the following:
  - Eltrombopag
  - Cyclosporine
  - Rabeprazole, pantoprazole, or any similar PPIs (except as noted in Section 5.9)

  Other BCRP inhibitors include lapatinib, elvitegravir and cobicistat, protease inhibitors, and several investigative drugs. All these are prohibited during the study for other reasons.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments for TGA (Table 6), TGB (Table 7), and TGC (Table 8), and the schedule of laboratory assessments (Table 9). Required analytes for laboratory tests are listed in Table 10 and Table 11, and timed assessments are provided in Table 12. See Section 7 for instructions on how to conduct and record each assessment.

Table 6: Schedule of Study Assessments – Treatment Group A (Part 1, Part 2, and Part 3)

Visit Day (Range) / Evaluation/Window	Section	Screening	Cohort 1 First 3 Subjects Only (Section 6.2.2)		Cycle 1[a]					Cycles 2 and Beyond			EOT	Follow -Up	
			D0	D0 + 1	D1	D2	D8	D15	D16	D1	D2	D11		Safety	Survival
		Day -28 to Day -1					± 3 Days			± 3 Days		± 4 Days	± 3 Days	EOT + 30 Days (+ 7 d)	EOT + Every 9 Weeks
Informed consent	7.1	X													
Inclusion/exclusion criteria	3	X	X		X										
Medical and cancer history	7.3.1	X													
Buccal swab	7.7.3.3	X													
Tumor tissue	7.7.3.1	X				Optional tumor biopsy during study, as medically indicated									
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	X	X		X[b]	X	X	
Administer INCB054329 in clinic[c]	7.8.1		X		X	X	X	X	X	C2[d]	C2[d]				
Contact IRT	7.2		X		X					X					
Drug dispense/compliance check	7.8.2				X		X	X		X			X		
Comprehensive physical exam	7.4.2	X											X	X	
Targeted physical exam	7.4.3		X	X	X	X	X	X		X					
ECOG performance status	7.6	X	X		X					X			X		
Vital signs/weight	7.4.4	X[e]	X	X	X	X	X	X		X			X	X	
12-lead ECG	7.4.5.1	X								X			X	X	
Timed 12-lead ECG	7.4.5.2		X		X			X							
AE assessment	7.4.1	X	X	X	X	X	X	X	X	X		X[b]	X	X	
Laboratory assessments[f]	7.4.6	X	X	X	X	X	X	X	X	X	C2[d]	X	X	X	
Efficacy/disease assessments	7.5	X			Every 9 weeks from baseline assessment (± 1 week) until disease progression or until new treatment is initiated.										
Provide reminder card	7.8.3	X	X	X	X	X	X	X	X	X			X		
Survival follow-up	7.8.4														X[b]

[a] For subjects in Part 2, study assessments including PK, timed 12-lead ECGs, safety laboratory assessments, targeted physical examinations, and vital signs/weight will follow the Cycle 1 schedule during the first 21 days after intrasubject dose escalation occurs.
[b] May conduct assessment by phone.
[c] On all other days, subjects will self-administer INCB054329 at home.
[d] First 12 subjects in Part 3 TGA will participate in the food effect study in Cycle 2 only. Food effect PK timepoints are as follows: 0.5, 1.0, 2, 4, 6, 8, and 24 hours postdose. See Section 7.7.1.3.
[e] Also record height at screening.
[f] Screen laboratory tests must be performed within 14 days before Cycle 1 Day 1. If screening laboratory tests are performed within 3 days of Cycle 1 Day 1, they do not need to be repeated for Cycle 1 Day 1.

Table 7: Schedule of Study Assessments – Treatment Group B (Part 1 and Part 3)

Visit Day (Range) / Evaluation/Window	Section	Screening	Cycle 1					Cycles 2 and Beyond		EOT	Follow-Up	
											Safety	Survival
		Day -28 to Day -1	D1	D2	D8	D15	D16	D1	D11		EOT + 30 Days (+ 7 d)	EOT + Every 9 Weeks
					± 3 Days			± 3 Days	± 4 Days	± 3 Days		
Informed consent	7.1	X										
Inclusion/exclusion criteria	3	X	X									
Medical and cancer history	7.3.1	X										
Buccal swab	7.7.3.3	X										
Bone marrow biopsy and aspirate[a]	7.5.1, 7.7.3.2	X	After 3, 6, and 12 months on study when required for response assessment or if clinically indicated									
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	X[b]	X	X	
Administer INCB054329 in clinic[c]	7.8.1		X	X	X	X	X					
Contact IRT	7.2		X					X				
Drug dispense/compliance check	7.8.2		X		X	X		X		X		
Comprehensive physical exam	7.4.2	X								X	X	
Targeted physical exam	7.4.3		X	X	X	X		X				
ECOG performance status	7.6	X	X					X		X		
Vital signs/weight	7.4.4	X[d]	X	X	X	X		X		X	X	
12-lead ECG	7.4.5.1	X						X		X	X	
Timed 12-lead ECG	7.4.5.2		X			X						
AE assessment	7.4.1	X	X	X	X	X	X	X	X[b]	X	X	
Laboratory assessments	7.4.6	X	X[e]	X	X	X	X	X	X	X	X	
Immunophenotyping[f]	7.5.2	X	When confirming response									
Efficacy/disease assessments	7.5	X	X			X			X	X		
Peripheral blood disease assessment[g]	7.5.3	X	X			X		X		X		
Provide reminder card	7.8.3	X	X	X	X	X	X	X		X		
Survival follow-up	7.8.4											X[b]

[a] Bone marrow biopsy and aspirate performed at screening and as clinically indicated or at Months 3, 6, 12, and yearly thereafter when required for response assessment. If archival aspirate is available and meets criteria described in Section 3.2, this may be omitted at screening. For AML subjects, bone marrow disease assessment during Cycle 2 is strongly recommended unless contraindicated.

[b] May conduct assessment by phone.

[c] On all other days, subjects will self-administer INCB054329 at home.

[d] Also record height at screening.

[e] Screen laboratory tests must be performed within 14 days before Cycle 1 Day 1. If screening laboratory tests are performed within 3 days of Cycle 1 Day 1, they do not need to be repeated for Cycle 1 Day 1.

[f] For subjects with AML leukemia, immunophenotyping should be performed at screening and to confirm response. If appropriate to the histologic subtype, immunophenotyping may be conducted in subjects with lymphoma as part of routine standard of care and/or at response assessment.

[g] Subjects will have peripheral blood disease status assessments at screening, Cycle 1 Day 1, Cycle 1 Day 15, Day 1 (± 3 days) of each subsequent cycle, and EOT and when clinically indicated. If indicated (ie, disease monitored by imaging), subjects with MF will have imaging assessments every 9 weeks using the appropriate imaging modality (eg, MRI or CT for spleen measurement).

Table 8: Schedule of Study Assessments – Treatment Group C (Part 2 and Part 3)

Visit Day (Range) / Evaluation/Window	Section	Screening	Cycle 1[a]					Cycles 2 and Beyond		EOT	Follow -Up	
											Safety	Survival
		Day -28 to Day -1	D1	D2	D8	D15	D16	D1	D11		EOT + 30 Days (+ 7 d)	EOT + Every 9 Weeks
					± 3 Days			± 3 Days	± 4 Days	± 3 Days		
Informed consent	7.1	X										
Inclusion/exclusion criteria	3	X	X									
Medical and cancer history	7.3.1	X										
Buccal swab	7.7.3.3	X										
Bone marrow biopsy and aspirate	7.5.1, 7.7.3.2	X[b]	Confirming CR and as clinically indicated									
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	X[c]	X	X	
Administer INCB054329 in clinic[d]	7.8.1		X	X	X	X	X					
Contact IRT	7.2		X					X				
Drug dispense/compliance check	7.8.2		X		X	X		X		X		
Comprehensive physical exam	7.4.2	X								X	X	
Targeted physical exam	7.4.3		X	X	X	X		X				
ECOG performance status	7.6	X	X					X		X		
Vital signs/weight	7.4.4	X[e]	X	X	X	X		X		X	X	
12-lead ECG	7.4.5.1	X						X		X	X	
Timed 12-lead ECG	7.4.5.2		X			X						
AE assessment	7.4.1	X	X	X	X	X	X	X	X[c]	X	X	
Laboratory assessments[f]	7.4.6	X	X[f]	X	X	X	X	X	X	X	X	
MM disease assessments[g]	7.5.1 7.5.4	X	X			X			X	X		
Skeletal survey	7.5.5	X	At investigator discretion									
Provide reminder card	7.8.3	X	X	X	X	X	X	X		X		
Survival follow-up	7.8.4											X[c]

[a] For subjects in Part 2, study assessments including PK, timed 12-lead ECGs, safety laboratory assessments, targeted physical examinations, and vital signs/weight will follow the Cycle 1 schedule during the first 21 days after intrasubject dose escalation occurs.
[b] If archival aspirate is available and meets criteria described in Section 3.2, this may be omitted at screening.
[c] May conduct assessment by phone.
[d] On all other days subjects will self-administer INCB054329 at home.
[e] Also record height at screening.
[f] Screen laboratory tests must be performed within 14 days before Cycle 1 Day 1. If screening laboratory tests are performed within 3 days of Cycle 1 Day 1, they do not need to be repeated for Cycle 1 Day 1.
[g] Multiple myeloma disease assessments as per Section 7.5.4 and Table 11 should be performed at screening, Cycle 1 Day 1, Cycle 1 Day 15 (± 3 days), Day 11 of each subsequent cycle (± 4 days), and EOT. If screening MM disease assessment is performed within 7 days of Cycle 1 Day 1, it does not need to be repeated.

Table 9: Schedule of Laboratory Assessments – All Treatment Groups

Visit Day (Range)	Section	Screening	TGA/Cohort 1 First 3 Subjects Only		Cycle 1					Cycles 2 and Beyond			EOT	Safety Follow-Up
			D0	D0 + 1	D1	D2	D8	D15	D16	D1	D2[a]	D11		
Evaluation/Window		Day -28 to Day -1								± 3 Days		± 4 Days	± 3 Days	EOT + 30 Days (+ 7 d)
Overnight fast before assessments			X		X			X		Even cycles				
Comprehensive blood chemistries	Table 10	X	X	X	X[b]	X	X	X		X		X	X	X
Hematology with differential	Table 10	X	X	X	X[b]	X	X	X		X		X	X	X
Coagulation panel	Table 10	X	X		X[b]		X			Even cycles			X	
Lipids	Table 10	X			X[b]		X			Even cycles			X	X
Urinalysis	Table 10				X		X	X		Even cycles			X	X
Serum pregnancy test	7.4.6.1	X	X[c]		X[c]									X
Hepatitis testing	7.4.6.2	X												
PK – plasma (untimed)	7.7.1.1									X			X	
PD – correlative[d]	7.7.3.6				X					X			X	
PD – plasma[d]	7.7.3.4		X		X			X		X			X	
Detailed schedule for the following assessments is shown in Table 12.														
PK – plasma (timed)	7.7.1.2		X	X	X	X	X[e]	X	X					
PK – food effect	7.7.1.3									C2[a]	C2[a]	First 12 subjects in Part 3 TGA only		
PD – whole blood[f]	7.7.3.5		X	X	X	X		X	X	C2[a]	C2[a]			
PK – urine	7.7.2							X						

[a] First 12 subjects in Part 3 TGA, Cycle 2 only. See Section 7.7.1.3.
[b] If completed 3 days before Cycle 1 Day 1, this laboratory assessment may be omitted.
[c] If serum pregnancy completed 3 days before Cycle 1 Day 1, a urine pregnancy test may be performed.
[d] Only collected at Cycles 2, 4, 7, 10, 13, and every third cycle thereafter.
[e] Predose only.
[f] Avoid scheduling on Fridays wherever possible, due to overnight shipment of whole blood samples.

Table 10: Laboratory Tests: Required Analytes

Blood Chemistries	**Hematology**	**Serology**[a]
Albumin Alkaline phosphatase ALT AST Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine HbA1c[b] Glucose Lactate dehydrogenase Magnesium Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is > ULN)[c] Total protein Uric acid	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count Differential count, including:[d] • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils • Blasts	Hepatitis B surface antibody Hepatitis B surface antigen Hepatitis B core antibody HBV-DNA HCV antibody HCV-RNA
		Pregnancy
		Female subjects of childbearing potential require a serum test at screening. Pregnancy tests (serum or urine) should be repeated during the study as required by local regulations.
		Coagulation
		Prothrombin time Activated partial thromboplastin time International normalized ratio
Lipids		**Urinalysis With Microscopic Examination**
Total cholesterol Triglycerides Low-density lipoprotein High-density lipoprotein		Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen

[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 only needs to be performed once during screening.
[c] Direct bilirubin should only be performed when total bilirubin is > 1.5 × ULN and the subject does not have Gilbert's syndrome.
[d] Absolute values must be provided for lymphocytes and neutrophils. Blasts readings are required at intervals specified in Table 7 for disease where peripheral blast count is part of disease assessments such as lymphoma, leukemia, MDS, MDS/MPN, and MF.

Table 11: Laboratory Tests: 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-free light chains • Beta-2 microglobulin
Baseline, Confirming CR, and as Clinically Indicated
• Bone marrow aspirate and biopsy • FISH/cytogenetics

FISH = fluorescence *in situ* hybridization.

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

Table 12: Timed Assessments

Visit	Assessment	Fasting Requirement	HOLD AM Dose			Time Postdose							
				Predose	Dose	0.5 h ± 5 min	1 h ± 15 min		2 h ± 15 min	4 h ± 15 min	6 h ± 30 min	8 h ± 30 min	24 h ± 30 min
Cohort 1 first 3 subjects													
Day 0[a] Section 6.2.2	ECG	Fast overnight	n/a	**3X**	♦			snack/ meal	X	X	X		
	PK plasma			≤ 15 min after ECG		X	X		≤ 15 min after ECG	≤ 15 min after ECG	X	X	X
	PD whole blood			≤ 15 min after ECG		X	X		≤ 15 min after ECG	≤ 15 min after ECG	X		
All treatment groups													
Day 1	ECG	Fast overnight	n/a	**3X**	♦			snack/ meal	X	X	X		
	PK plasma			≤ 15 min after ECG		X	X		≤ 15 min after ECG	≤ 15 min after ECG	X	X	X
	PD whole blood			≤ 15 min after ECG		X	X		≤ 15 min after ECG	≤ 15 min after ECG	X		
Day 2 Day 0 + 1[a] C1D16	PK plasma	none	X	X	♦								X
	PD whole blood			X									
C1D8	PK plasma	none	X	X	♦								
C1D15	ECG	Fast overnight	X	**3X**	♦			snack/ meal	X	X	X		
	PK plasma			X		X	X		X	X	X	X	X
	PD whole blood			X		X	X		X	X	X		
	Urine PK			void		Collect urine over 8 hours following study drug administration.							
Part 3 TGA only: first 12 subjects (food effect)													
C2D1[b]	PK plasma	Fast overnight	X[b]	X	♦	X	X		X	X	X	X	X
	PD whole blood			X		X	X		X	X	X		
C2D2	PK plasma	none	X	X	♦								
	PD whole blood												

[a] First 3 subjects in Part 1 TGA Cohort 1 only.
[b] High-fat meal to be consumed within a 25-minute period, followed by study drug administration within 5 minutes of completing the meal.

6.1. Screening Period

The screening period is the interval, up to a maximum of 28 days duration, between the signing of the ICF and the day that the treatment period begins (Day 1, or Day 0 as applicable, see Section 6.2). Informed consent must be obtained before performing any study-specific procedures. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during this period.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before randomization or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during the screening period if the investigator believes the results to be in error. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status (eg, following recovery from an infection).

6.2. Treatment Period

6.2.1. Day 1

The treatment period begins on the day the subject receives the first dose of study drug; this is defined as **Cycle 1 Day 1** (except Cohort 1 as noted below) and continues until a decision is made to permanently discontinue the study drug. At Cycle 1 Day 1, results from screening period assessments should be reviewed to determine whether the subject continues to meet the eligibility requirements as specified in the Protocol. See Section 7.4.6 for discussion of the timing of tests performed at Day 1.

6.2.2. Day 0 (Part 1 TGA Cohort 1 Only)

The first 3 subjects in Part 1 TGA Cohort 1 will be administered INCB054329 as a single dose of 5 mg, followed by a timed PK analysis to confirm exposure; this will be identified as Day 0. No further study drug will be dispensed or administered on Day 0. Subjects will also return to the clinic the following day (Day 0 + 1) to collect safety laboratory samples and a 24-hour PK sample. Cycle 1 Day 1 will begin for a given subject when the PK analysis for that subject is complete; this is expected to be 7 to 10 days after Day 0.

6.2.3. Visit Scheduling

Please note that unless it is unavoidable, the Day 1 and 15 study visits should not be conducted on Fridays or on the day before a national holiday, as fresh PD samples will be shipped overnight to the sponsor on the day of these visits.

Dates for subsequent study visits will be determined based upon Cycle 1 Day 1 and should occur within ± 3 days of the scheduled date unless delayed for safety reasons. If study drug administration must be interrupted at the beginning of a new planned cycle, the cycle will be delayed until the study drug can be restarted. All planned assessments are shown in Table 6 through Table 12. Other clinical assessments, or PK/PD assessments, may be added if medically indicated or indicated by emerging data, to maintain safety.

The visit on Day 11 of Cycle 2 and beyond is scheduled to assess safety and disease status in select malignancies only and is primarily a laboratory-only visit. If the investigator deems there

is no medical need for the subject to be seen by the clinic staff, AEs and concomitant medication check may be conducted by phone contact with the subject.

6.3. 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 should be entered as "unscheduled" visits in the eCRF. The sponsor may also request additional visits to be performed, if needed, based upon emerging safety data.

6.4. End of Treatment

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

6.5. Follow-Up Period

6.5.1. 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 37 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 serious adverse events (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.

6.5.2. Survival Follow-Up

After the subject has reached EOT (permanently discontinuing the study treatment), the survival follow-up period will begin. See Section 7.8.4 for information to be collected during this period.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

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

7.2. Interactive Response Technology Procedure

The investigator or designee will assign a subject ID number when a subject enters the screening period. 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.

7.3. Demography and History

7.3.1. Demographics and Medical History

Demographic data and a complete medical and medication history will be collected at screening. This will include a detailed history of prior medical and surgical therapies for the disease under study.

7.3.2. Prior and Concomitant Medications

Prior and concomitant (ongoing) medications will be reviewed to determine study eligibility. The medication record will be maintained after enrollment as documentation of 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, which begins 30 days before Day 1 and continues through 30 days after the last dose of study drug.

7.4. Safety Assessments

7.4.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed routinely for the occurrence of AEs during scheduled clinic visits. Additionally, AEs may also be reported by subjects during phone contact in between clinic visits, or after treatment discontinuation. 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.

7.4.2. Comprehensive Physical Examination

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

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

7.4.3. Targeted Physical Examination

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

7.4.4. Vital Signs and Body Weight/Height

Vital sign measurements (blood pressure, pulse, respiratory rate, and body temperature) will be taken with the subject in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Body weight will also be measured. Height will be recorded at screening only.

7.4.5. Twelve-Lead Electrocardiograms

A central ECG vendor will be used. The 12-lead ECGs will be interpreted by the investigator at the site for immediate subject management. The trace will also be transmitted to the central ECG vendor for analysis by a central reader, and data archiving. 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 should be reported as an AE.

7.4.5.1. Electrocardiogram Procedures

All 12-lead ECGs will be performed with the subject in a recumbent position after 5 minutes of rest and should not be performed within 15 minutes after a blood collection.

7.4.5.2. Additional Instruction for Timed Electrocardiograms

Timed ECGs will be conducted before the clinic administration of study drug (**predose**) and using the schedule shown in Table 12. Electrocardiograms conducted before administration (establishing the baseline for the day) should be performed in triplicate (see Table 12). The ECGs should be conducted before, but within 15 minutes of, the PK blood collection at the corresponding timepoint. The specified postdose timepoints may be adjusted based upon emerging PK data.

7.4.6. Laboratory Assessments

A laboratory local to the study site and subject will perform all clinical laboratory assessments for safety. The investigative site will enter the local laboratory results and laboratory normal

ranges into the eCRF. All local laboratory assessments (ie, blood chemistries, hematology assessments, coagulation tests, lipid testing, and urinalysis) should be performed using standard procedures on the days indicated in Table 9. Table 10 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. Laboratory samples collected for the Day 1 evaluation must be performed before dose administration on Day 1 or no more than 3 days before Day 1 dose administration. (This also applies to Day 0 for TGA/Cohort 1.) After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study drug administration (within the 3-day study window), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

7.4.6.1. Pregnancy Testing

Serum pregnancy tests, performed and analyzed by the site laboratory, are required before first dose of study drug as shown in Table 9. Subsequently, pregnancy tests (either serum or urine) may be conducted as medically indicated or as required per local guidelines.

If a subject inadvertently becomes pregnant while on treatment with INCB054329, the subject will immediately be withdrawn from treatment (see Section 8.5). The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the sponsor without delay and within 24 hours if the outcome is an SAE (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the sponsor and followed as described above and in Section 8.

7.4.6.2. Serology (Hepatitis Testing)

Testing for hepatitis (detailed in Table 10) is required at screening, and results should 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 needed to obtain the results. If hepatitis B and/or C serology are positive, subjects will be required to undergo additional testing for HBV-DNA and HCV-RNA by PCR assay to assess active infection. Subject 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 IgM and positive HBV antibody; these subjects would have low risk of liver damage.

7.5. Efficacy/Disease Assessments

Objective assessment of disease status is required, using appropriate disease-specific techniques, and the investigator's assessment will be used to determine responses and will be logged into the eCRF.

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

- AML: International Working Group Response Criteria for Acute Myeloid Leukemia (Cheson et al 2003; Appendix F)
- Lymphoma: Response Criteria For Lymphoma – The Lugano Classification (Cheson et al 2014; Appendix L)
- MDS: International Working Group Response Criteria For Myelodysplastic Syndrome (Cheson et al 2006; Appendix G)
- MDS/MPN: International Consortium Proposal of Uniform Response Criteria for Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) In Adults (Savona et al 2015; Appendix H)
- MF: International Working Group–Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report (Tefferi et al 2013; Appendix I)
- MM: International Uniform Response Criteria for Multiple Myeloma (Durie et al 2006; Appendix J)
- 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 (Blade et al 1998; Appendix K)
- Solid tumors: RECIST 1.1 (Eisenhauer et al 2009)

Efficacy assessments will be performed at screening (this will be considered the baseline disease assessments) and at the intervals defined in Table 6, Table 7, and Table 8 throughout the study. For diseases routinely assessed through imaging studies (ie, solid tumors, lymphoma, and MF [as applicable]), cycle delays should not interrupt the 9-week scan interval; thus tumor assessments and cycles may become out of sync. Subjects in all treatment groups/cohorts who discontinue treatment for reasons other than disease progression should continue to have disease assessments performed and recorded every 9 weeks until they have experienced disease progression or started another treatment.

7.5.1. Leukemia, MDS, MDS/MPN, MF, Lymphoma, and Multiple Myeloma: Bone Marrow Examination for Assessment of Disease Status

Bone marrow examination (aspirate and biopsy) is required at screening for subjects with diseases that are typically monitored though bone marrow examination, including leukemia, MDS, MM, MDS/MPN, and MF (bone marrow examination may be omitted if the criteria listed in Section 3.2 are met). If disease status requires assessment with bone marrow aspirate or biopsy, subjects with leukemia, MDS, MDS/MPN, or MF should 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 11 (± 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.

Subjects with MM only require a bone marrow examination to confirm CR, after 2 consecutive laboratory disease assessments (Table 11) demonstrating negative serum and/or urine immunofixation, and as clinically indicated.

Subjects with lymphoma will not require a bone marrow examination at baseline if the subject had a bone marrow examination performed after the most recent prior therapy and/or a baseline PET or PET/CT shows that the subject does or does not have disease in the bone marrow in a patient with PET-avid disease. If one of these conditions does not apply, a baseline bone marrow biopsy is required unless it would not affect disease assessment and medical monitor approval is obtained. On-study bone marrow examinations are required if needed to confirm response.

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

7.5.2. Immunophenotyping: Leukemia and Lymphoma

For subjects with leukemia, 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 may be conducted in subjects with lymphoma as part of routine standard of care and/or at response assessment. Results will be captured in the eCRF.

7.5.3. Leukemia, MDS, and MDS/MPN: Peripheral Blood Blast Counts

For disease assessment timepoints in leukemia, MDS, and MDS/MPN that do not correspond to a bone marrow examination, 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) in determining disease status.

7.5.4. Multiple Myeloma: Disease Assessment

Multiple myeloma laboratory assessments should be performed as per Table 8 and Table 11. Test samples should be drawn or collected and brought in (eg, 24-hour urine, as applicable) for all of these tests at screening, Cycle 1 Day 1, Cycle 1 Day 15 (± 3 days), Day 11 of subsequent cycles (± 4 days), and EOT to assess for response status. In addition, a bone marrow examination (aspirate and biopsy) will be required to confirm CR.

7.5.5. Multiple Myeloma: Skeletal Survey

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

7.6. Performance and Quality-of-Life Assessments

Performance status will be assessed using the ECOG performance status scale (Appendix C), according to the study schedule (Table 6, Table 7, and Table 8). Quality-of-life assessment questionnaires will not be used in this study.

7.7. Pharmacokinetic Assessments

7.7.1. Blood Sample Collection

Pharmacokinetic samples will be obtained at the visits indicated in the table of Laboratory Assessments (see Table 9) to evaluate plasma PK parameters as described in Appendix B. For PK sample collection, the following will be recorded:

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

Subjects will receive reminder cards in advance of the study visit providing instructions to prepare for the visit (see Section 7.8.3). Instructions for plasma preparation and sample shipping will be provided in the Laboratory Manual.

7.7.1.1. Untimed Pharmacokinetic Testing

On days when the timing of plasma PK blood collection is not specified, the sample may be collected at any time during the study visit, irrespective of the time that the study drug was taken that day. An effort should be made to vary the time between the last dose of study drug and the time of collection, from visit to visit.

7.7.1.2. Timed Pharmacokinetic Testing

Timed PK testing will be performed using the timepoints shown in Table 12. The timing of PK sample collection may be coordinated with other timed tests (PD testing or ECG). On these study dates, the subject should arrive at the research unit in the morning. If study drug has been previously dispensed, the reminder card (see Section 7.8.3) will remind the subject to refrain from taking the study drug at home that day. Subjects will also be reminded about fasting requirements, as applicable (see Table 12). A trough (predose) PK sample will be collected early in the study visit, followed by administration of the study drug and subsequent timed blood samples. The study drug will be administered with 240 mL of water. Subjects should remain fasting from food or water for at least 1 hour postdose, after which a meal or snack may be consumed.

Refer to the Laboratory Manual for PK timepoint sample collections. Additional adjustments to the timing of postdose blood collection may be made based upon emerging PK/PD data, and additional sampling may be performed if emerging data suggest that drug exposure confirmation is required for subject safety; however, no more than 6 postdose timepoints will be used on a given day.

7.7.1.3. Food-Effect Pharmacokinetic Testing

Pharmacokinetic testing for food effect on drug exposure will be performed on a subgroup of the first 12 subjects enrolled in Part 3 TGA, Cycle 2 only. 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. Refer to the Laboratory Manual for PK timepoint sample collections.

7.7.1.4. Bioanalytical Methodology

Plasma samples will be analytes by the sponsor, or 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 9.4.5.

7.7.2. Urine Sample Collection

Urine will be collected from each subject at Cycle 1 Day 15 after administration of INCB054329 and a predose void. Total urine will be collected over an 8-hour interval following study drug administration. Urine containers should be kept at reduced temperature (refrigerated or ice bath) during collection. After the interval, urine should be mixed thoroughly. The total urine volume and the pH should be measured and recorded in the individual eCRF. Shipping and handling instructions will be provided in the Laboratory Manual; samples will be analyzed by the sponsor or its designee for parameters described in Appendix B.

7.7.3. Pharmacodynamic [redacted]

7.7.3.1. Tumor Biopsy (Treatment Group A)

Subjects must have an archival tumor biopsy sample (obtained within the last year and after the last systemic treatment) or prior FoundationOne® HEME (Foundation Medicine, Inc., Cambridge, MA) available or be willing to undergo a pretreatment tumor biopsy at baseline. A minimum of 15 slides must be available (25 are requested). If prior FoundationOne®

(Foundation Medicine, Inc., Cambridge, MA) data are available and obtained using the tumor biopsy sample met the criteria as described above, less than 15 slides will be sufficient after discussing with the medical monitor. 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. Details and methods for obtaining, processing, and shipping the fresh tumor biopsy samples and for processing and shipping the archived tumor tissue samples will be provided in the Laboratory Manual for the study.

Tumor lesions used for biopsy should not be selected as response assessment target lesions, unless there are no other lesions suitable. If a response assessment target lesion is used for biopsy, the lesion must be ≥ 2 cm in the longest diameter.

Optional fresh tumor tissue biopsy specimens may be obtained at any time during the study in subjects with accessible tumors to assess intratumoral changes that might be associated with safety, response, or resistance to treatment. When a tumor biopsy is obtained on study, a sample of peripheral whole blood will also be collected for correlative studies.

7.7.3.2. Bone Marrow Aspirate for PD [redacted] Assessment (Treatment Groups B and C)

Subjects must have an archival bone marrow aspirate sample (obtained within 1 year of the start of treatment) available or be willing to undergo collection of a pretreatment sample at baseline. A minimum of 1.5 mL of sample must be available. Archival material from the same sample used for baseline disease assessment may be provided if the requirements in Section 7.5.1 are met, or it may be from another sample collected in the prior year. Details and methods for obtaining, processing, and shipping the fresh aspirate samples and for processing and shipping archived samples will be provided in the Laboratory Manual for the study.

Optional fresh bone marrow specimens may be obtained at any time during the study in subjects to assess changes that might be associated with safety, response, or resistance to treatment.

7.7.3.3. Buccal Swab

A buccal swab will be performed at screening on all subjects with hematological malignancies as a source of nontumor genetic material. Details of collection and shipping will be provided in the Laboratory Manual.

7.7.3.4. Plasma Pharmacodynamics

Pharmacodynamic samples will be collected according to the schedule shown in Table 9. Plasma will be isolated from these samples at the investigative site, using materials provided and instructions found in the Laboratory Manual; samples should be frozen and shipped as directed.

7.7.3.5. Whole Blood Pharmacodynamics

Whole blood PD samples will be generally collected in conjunction with the timed PK samples (see Table 12) for the measurement of drug effect (BET inhibition as evidenced by inhibition of c-Myc). These samples must be shipped directly (unfrozen) to the sponsor, on the day of collection, for processing and analysis. Please see the Laboratory Manual for detailed collection, handling, and shipping instructions.

Visits that include PD whole blood collection (see Table 9 and Table 12) should not, unless unavoidable, be conducted on Fridays or on the day before a national holiday, since fresh PD samples will be shipped overnight to the sponsor on the day of these visits.

7.7.3.6. Whole Blood Correlative Studies

Whole blood for correlative PD analysis will be collected as shown in Table 9. The Laboratory Manual will provide detailed collection, handling, and shipping instructions.

7.7.3.7. Analyses

Tumor biopsy samples will be used by the sponsor, or 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]

7.8. Other Study Procedures

7.8.1. Administration of Study Drug in the Clinic

Study drug will be administered in the study clinic on days when it is necessary to collect a trough (predose) sample and when timed postdose samples are collected (Table 9 and Table 12). Subjects should be given INCB054329 with 240 mL of water, and the exact time of the dose will be recorded. All other days, the subject will self-administer the study drug at home.

7.8.2. Dispensing Study Drug and Assessing Compliance

Unless specified as a day for in-clinic administration, the subject will self-administer INCB054329 orally, with water, according to the dose and schedule prescribed by the investigator, from a supply dispensed by the investigative site. An initial bulk supply of INCB054329 will be provided to investigative sites before enrollment of the first subject. Thereafter, the site staff will contact the IRT for resupply of INCB054329. When dispensing to subjects, the investigator or designee will remove the appropriate quantity of study drug from their stock, dispense the medication, and enter the amount dispensed into the eCRF and drug accountability log. The study subject will return all full, empty, and opened/partially used

bottles of study drug at the beginning of each treatment cycle, and a compliance check (tablet count) will be performed by the clinic staff at each visit indicated in Table 6, Table 7, and Table 8; therefore, appropriate steps should be taken to optimize compliance. Each time the study drug is dispensed (or dose adjustment made), the IRT must be contacted (see Section 7.2) to maintain supply management.

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

- Store the study drug at room temperature, in a safe place, out of the reach of children.
- Only remove from the bottle the amount of tablets needed at the time of administration. (Do not remove doses in advance of the next scheduled dose.)
- When taking the study drug at home, take the tablets with a glass of water, on an empty stomach each morning, or at least 2 hours after the last meal. It is preferable to refrain from food or drink (other than water) for 1 hour after the dose.
- If vomiting occurs after taking study drug, the vomited dose should not be replaced; simply take the study drug at next scheduled time.
- Make every effort to take doses on schedule. Generally the drug should be taken in the morning, but if missed at that time, it can be taken later the same day.
- Report any missed doses.
- Bring all used and unused study drug bottles to the site at each visit.

7.8.3. Distribution of Subject Reminder Cards

Subjects will be provided with subject reminder cards at each visit indicated in Table 6, Table 7, and Table 8. The reminder card should supplement other written instructions that do not change from visit to visit (see Section 7.8.2) with information that will guide the subject in between specific study visits, such as:

- Dose instructions for study drug (ie, number of tablets to be taken during the current cycle). Note that extra caution and instruction may be required if there is more than 1 dose strength needed to achieve the required dose.
- Instructions for taking any prescribed concomitant medications.

The reminder card should also provide instructions regarding the next study visit:

- The date and time of the next visit.
- Whether to TAKE or HOLD the morning dose of study drug before coming to the clinic.
- Whether or not to fast overnight before the visit.

The reminder card may also contain fields for the subject to record certain information such as the following:

- The date and time of the last dose taken before the visit (this could be the morning of the visit or on the prior day, for Days 8 and 15 for example).
- Dates of any known missed doses.

7.8.4. Survival Follow-Up

During this period, survival status and information on current anticancer therapies should be obtained at least every 9 weeks following EOT. Clinic records may be used as a reference if the subject is still under the investigator's care. Alternatively, the subject should be contacted by telephone or email periodically from EOT until death, or the end of the study, whichever occurs first. Attempts at contact should be made before the end of the 9-week interval, in anticipation of delayed communication. A delay in subject response will not be considered a deviation; however every attempt should be made to successfully complete contact with the subject.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

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

"Disease progression" and events related to disease progression (based on investigators judgement), including death due to disease progression, should not be recorded as an AE or SAE. For example, if it is determined that disease progression resulted either in hospitalization, a life-threatening event, or death, then the specific event(s) that led to the subject's hospitalization, life-threatening event, or death should be reported as the AE(s) instead of "disease progression."

Adverse events will be assessed according to the CTCAE v4.03. The CTCAE Grade 5 severity (death) will not be used in this study; rather, AEs with an outcome of death will be reported as CTCAE Grade 4. Adverse events leading to death will be recorded with the outcome of the event as "fatal." If an event is not classified by CTCAE, the severity of the AE will be graded according to the Protocol-defined toxicity criteria and 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).
- The reasonable possibility that the AE is related to the study treatment: related (yes) or unrelated (no).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event SAE definition provided in Section 8.3.1.

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

All AEs should be treated appropriately. If a concomitant medication or nondrug therapy is given, this action should be recorded on the AE and Prior/Concomitant Medications 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 it, 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, which 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. For analysis purposes, this will be considered 1 AE for this subject and the maximum severity will be used.

8.2. Laboratory Test Abnormalities

8.2.1. Definitions and Reporting

Laboratory abnormalities that constitute an AE in their own right (are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug), should be recorded on the AE page of the 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, and/or per the investigator's discretion. A dose modification for the laboratory abnormality may be required (see Section 5.6) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

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

- Is fatal or life-threatening (ie, immediate risk of dying).
- Results in persistent or significant disability or incapacity.
- Constitutes a congenital anomaly or birth defect.
- Is clinically meaningful (ie, defined as an event that jeopardizes the subject or requires potential medical or surgical intervention to prevent 1 of the outcomes listed above).
- Is considered meaningful by the investigator as an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.
- 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 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 given above and not resulting in hospital admission.

- Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, or where there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere.

8.3.2. Reporting

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has signed the ICF and up to the last study visit, or up to 30 days after the subject has stopped study treatment, whichever is later, must be reported to the sponsor (or designee) within 24 hours of learning of its occurrence. Any SAEs 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. Recurrent episodes, complications, or progression of the initial SAE must be reported as the follow-up to the original episode within 24 hours of the investigator receiving the information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. Previously planned (before providing informed consent) surgeries should not be reported as SAEs unless the underlying medical condition worsens over the course of the study.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report form of the eCRF. The investigator must assess and record the relationship of each SAE to each specific study drug when there is more than 1, complete the SAE Report Form in English, and send the completed and signed form to the sponsor or its designee within 24 hours. The investigator must assess if there is a reasonable possibility that the SAE is related to the study treatment: related (yes) or unrelated (no).

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

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

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

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

- The investigator must notify the sponsor or its designee immediately.
- The study drug must be discontinued immediately (female subjects only; see Section 5.6.1 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Pregnancy Initial and Follow-Up Report forms (as described below) to the sponsor or its designee.

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

8.6. Warnings and Precautions

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

8.7. Data Monitoring Committee

Not applicable. Safety data will be activity monitored by the sponsor in conjunction with the study investigators.

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 and any associated AEs via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information.

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 safety/efficacy evaluable population includes all subjects enrolled in the study who received at least 1 dose of study drug (INCB054329).

The PK/PD evaluable population includes subjects having received at least 1 dose of INCB054329 and had at least 1 PK/PD sample collected and analyzed. Data listings of study drug administration and sample records will be examined to identify subjects to be excluded from analyses of PK and/or PD data.

9.2. Selection of Sample Size

Part 1 of the study is a standard dose-escalation design, and the sample size depends on the occurrence of safety findings as defined by DLT criteria. Approximately 3 to 6 subjects will be enrolled in each cohort. Using this design, the probability of dose escalation for various DLT rates is given in Table 13.

Table 13: Probability of Dose Escalation by DLT Rate

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

For Part 2, at least 5 and up to 10 subjects per treatment group will be enrolled to investigate the feasibility of intrasubject dose titration in select solid tumors and lymphoma and multiple myeloma. For Part 3, approximately 5 subjects will be enrolled for each tumor type (with the exception of the group including any tumor with a known aberration in c-MYC or other genes in

which BET proteins are relevant, which will enroll 20 subjects) providing a > 80% chance of observing at least 1 responder if the underlying response rate is 30%.

9.3. Level of Significance

All statistical analyses are exploratory. Unless otherwise specified, all confidence intervals (CIs) provided will be at the 95% confidence level.

9.4. Statistical Analyses

Study endpoints will be evaluated using SAS® procedures for the generation of all tables, graphs, and statistical analyses. Continuous variables will be summarized using means, medians, standard errors, minimums, and maximums. Categorical variables will be summarized using frequency counts and percentages.

9.4.1. Definitions

Day 1 is the date at which the subject receives the first dose of study drug intended for continuous administration. Baseline assessments are defined as the last nonmissing value before the first dose of study drug (on Day 1).

9.4.2. Primary Analyses

The clinical safety data (vital signs, ECGs, routine laboratory tests, and AEs) will be summarized using descriptive statistics (eg, mean, frequency, standard deviation, range) using the safety population. Subject enrollment, disposition, demographics, and medical history will be summarized at baseline. The rate of DLTs will be summarized for each cohort. Dose exposure and intensity will be calculated for each cohort. Safety and disease response data will be compared over time to assess change from baseline. Pharmacokinetic and PD data will be analyzed with appropriate standard nonlinear analytic software.

9.4.2.1. Adverse Events

Adverse events will be tabulated by the MedDRA® preferred term and system organ class. Severity of AEs will be based on the CTCAE v4.03 criteria (NCI 2010). 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. Adverse events for the first cohort in Part 1 will be summarized separately.

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 CTCAE grades for AEs (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 once for the worst grade observed postbaseline.
- Shift tables using CTCAE grades to compare baseline to the worst postbaseline value will be produced with CTCAE grade.
- For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value will be produced 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 at each assessment time. Subjects exhibiting clinically notable vital sign abnormalities (see Table 14) 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 14: Criteria for Clinically Notable Vital Signs Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 45 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. Subjects exhibiting clinically notable abnormalities according to predefined criteria (see Table 15) will be listed.

Table 15: Criteria for Clinically Notable Electrocardiograms

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

9.4.3. Secondary Analyses

9.4.3.1. Efficacy Analyses

Efficacy endpoints will be analyzed using the efficacy evaluable population. The cohort in Part 1 having the same dose as the cohort in Part 2 may be pooled together with subjects in Part 2 for analysis, other cohorts in Part 1 will only be tabulated with summary statistics.

Efficacy endpoints include the following:

- The proportion of subjects who meet ORR criteria will be estimated with 95% confidence interval.
- The DOR is defined as the difference between the end of response and the start of response for subjects who have at least 1 response measurement. Subjects who discontinued before the end of the study or who are still responding at the time of data cut off will be censored at the last adequate assessment. The DOR will be assessed using the Kaplan-Meier method if there are enough observations.
- The PFS will be determined from the enrollment date until the earliest date of disease progression, as measured by investigator assessment, or death due to any cause. Subjects with no observed death or progression, or discontinued from the study without disease progression, will be censored at the date of last adequate assessment visit; PFS will be estimated using the Kaplan-Meier method if there are enough observations.
- The OS will be defined as number of days from enrollment date to the date of death. Subjects with no observed death will be censored at their last date known to be alive. The OS will be estimated using the Kaplan-Meier method if there are enough observations.

9.4.4. Pharmacodynamic Analyses

All PD data will be tabulated with summary statistics.

9.4.5. Pharmacokinetic Analyses

Pharmacokinetic analysis of INCB054329 including C_{max}, T_{max}, C_{min}, $AUC_{0\text{-}t}$, and Cl/F (Appendix B) will be performed on samples collected at the specified timepoints. The parameters will be calculated from the blood plasma concentrations of INCB054329 using standard noncompartmental (model-independent) PK methods and commercial software (Appendix B). The PK parameters will be summarized by descriptive statistics by part and cohort. The log-transformed PK parameters will be compared among the dose levels by using a 1-factor ANOVA. Dose-dependent parameters (C_{max} and AUC) will be normalized to the lowest common dose before statistical comparisons. C_{max} and AUC will be evaluated using a power model, eg, $AUC = \alpha \cdot (dose^{\beta})$ or equivalently, $\log(AUC) = \log(\alpha) + \beta \cdot \log(dose)$, where linear dose proportionality is accepted if β is not significantly different from 1. Attainment of steady state will be assessed separately for each cohort by comparing trough plasma concentrations on Days 8 and 15. For the food-effect assessment, the log-transformed PK parameters will be compared between the fed and fasted treatments using an ANOVA 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. Population PK methods may be employed if there are a sufficient number of plasma PK samples.

9.5. Analysis for 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 have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol; GCPs as defined in Title 21 of the US Code of Federal Regulations Parts 50, 54, 56, 312, and Part 11; ICH E6 GCP consolidated guidelines; and other local regulatory requirements as applicable to the study location(s). 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.
  - Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined monitoring plan. The investigator must allow the study monitors to review all study materials and subject records at each monitoring visit.
  - 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 authorities may visit the investigator at any time during the development of an investigational product to conduct an inspection of the study and the site. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the 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.
  - 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 approve all changes to site-specific ICFs. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.

- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - When the sponsor or its designee provides the investigator with a safety report, the investigator is responsible for ensuring that the safety report is 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, the investigator may assign some of the drug accountability duties to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee 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 correct

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

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 the end of the study (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 must (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; 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 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 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 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. LITERATURE REFERENCES

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods have been determined to be highly effective methods of contraception or birth control as defined in ICH (M3). These are more than 99% effective (< 1% failure rate per year when used consistently and correctly) (Trussell 2004) and are permitted under this Protocol for use by the subject and his/her partner:

- Complete abstinence from sexual intercourse
  - Only if in line with the preferred and usual lifestyle of the subject.
  - Periodic abstinence (eg. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Double barrier methods
  - Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository are acceptable.
  - A female condom and male condom should not be used together as friction between the 2 can result in either product failing.
- Birth control patch or vaginal ring
- Established oral, injectable, or implanted hormonal methods of contraceptives
- Intrauterine system (IUS) or intrauterine device (IUD)

APPENDIX B. PHARMACOKINETIC ANALYTICAL PARAMETERS

C_{ave}	Average steady-state plasma concentration (AUC_{0-12h}/12h or AUC_{0-24h}/24h)
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration during the dosing interval
T_{max}	Time to maximum plasma concentration
AUC_{0-t}	Area under the single-dose plasma concentration-time curve from Hour 0 to the last quantifiable measurable plasma concentration, calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
$AUC_{0-\tau}$ (ie, AUC_{0-12h} or AUC_{0-24h})	Area under the steady-state plasma concentration-time curve over 1 dosing interval (ie, from Hour 0 to 12 for twice-daily 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 INCB054329 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)

APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE 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. CYP3A4 INHIBITORS AND INDUCERS

Source: University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org. Accessed October 2016. Highlighted rows indicate recent additions to the list.

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
aprepitant	Antiemetics	80-125 mg QD (5 days)	midazolam	**3.29**	12891225	2003 Aug
casopitant	Antiemetics	120 mg QD (14 days)	midazolam	**3.13**	20840445	2010 Oct
amprenavir	Protease Inhibitors	1200 mg BID (10 days)	rifabutin	**2.93**	11158747	2001 Feb
faldaprevir	Antivirals	240 mg BID (14 days)	midazolam	**2.92**	25449227	2015 Apr
imatinib	Antineoplastic Agents	400 mg QD (7 days)	simvastatin	**2.92**	14612892	2003 Nov
verapamil	Calcium Channel Blockers	80 mg TID (2 days)	midazolam	**2.92**	8198928	1994 Mar
netupitant	Antiemetics	300 mg single dose	midazolam	**2.44**	23729226	2013 Oct
nilotinib	Kinase Inhibitors	400 mg BID (12 days)	midazolam	**2.4**	25418605	2015 Apr
grapefruit juice	Food Products	240 mL QD (4 days)	midazolam	**2.39**	10546919	1999 Oct
tofisopam	Benzodiazepines	100 mg TID (9 days)	midazolam	**2.36**	17989974	2008 Jan
cyclosporine	Immunosuppressants	Not provided (1-5 years)	midazolam	**2.21**	21753749	2011 Sep
ACT-178882	Renin Inhibitors	300 mg QD (14 days)	midazolam	**2.19**	22849770	2013 Dec

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ciprofloxacin[4]	Antibiotics	500 mg single dose	sildenafil	2.12	16372380	2005 Dec
schisandra sphenanthera	Herbal Medications	3 capsules (= 11.25 mg deoxyschizandrin) BID (7 days)	midazolam	2.05	19552749	2009 May
isavuconazole	Antifungals	clinical dose (detail not provided)	midazolam	2.03	NDA # 207500	2015
cimetidine	H-2 Receptor Antagonists	200-400 mg QID (1.5 days)	midazolam	2.02	6152615	1984 Sep
FK1706	Central Nervous System Agents	60 mg QD (14 days)	midazolam	2.01	19889885	2010 Feb
Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2)						
tabimorelin	Hormone Replacement	2.86-3.21 mg QD (7 days)	midazolam	1.93	12610745	2003 Feb
ranolazine	Cardiovascular Drugs	1000 mg BID (7 days)	simvastatin	1.89	NDA # 021526	2006
amlodipine	Calcium Channel Blockers	10 mg QD (9 days)	simvastatin	1.8	23965645	2014 Apr
lomitapide	Other Antilipemics	60 mg QD (7 days)	simvastatin	1.77	24734312	2014 Mar
fosaprepitant (IV)	Antiemetics	150 mg single 30-min infusion	midazolam	1.76	21209230	2011 Dec
Seville orange juice	Food Products	240 mL single dose	felodipine	1.76	11180034	2001 Jan
amiodarone	Antiarrhythmics	400 mg QD (4 days)	simvastatin acid	1.76	17301736	2007 May
chlorzoxazone	Muscle Relaxants	250 mg single dose (part of a 6-drug cocktail)	midazolam	1.68	11736864	2001 Nov
M100240	Antihypertensive Agents	50 mg single dose	midazolam	1.66	15051745	2004 Apr
fluvoxamine	Antidepressants	50-00 mg BID (12 days)	midazolam	1.66	14551182	2003 Nov
ranitidine	H-2 Receptor Antagonists	150 mg BID (1.5 days)	midazolam	1.66	6135440	1983 Jun
fostamatinib[5]	Anti-inflammatory Drugs	100 mg BID (7 days)	simvastatin	1.64	26748647	2016 Mar
goldenseal	Herbal Medications	1,323 mg (= 24.1 mg isoquinoline alkaloids) TID (14 days)	midazolam	1.63	17495878	2008 Jan
clotrimazole	Antifungals	10 mg TID (5 days)	midazolam	1.61	20233179	2010 Feb
tacrolimus	Immunosuppressants	Not provided (1-5 years)	midazolam	1.61	21753749	2011 Sep
palbociclib	Kinase Inhibitors	125 mg QD (8 days)	midazolam	1.58	NDA # 207103	2015
cilostazol	Antiplatelets	100 mg BID (7 days)	lovastatin	1.56	10702889	1999
ticagrelor	Antiplatelets	180 mg bid (7 days)	simvastatin	1.56	NDA # 022433	2011
peppermint oil	Food Products	600 mg (= 300 uL peppermint oil) single dose	felodipine	1.55	12235445	2002 Sep
ivacaftor	Cystic fibrosis treatments	150 mg BID (6 days)	midazolam	1.54	25103957	2015 Jan
GSK2248761	Transcriptase Inhibitors	100 mg QD (12 days)	midazolam	1.54	22288567	2012 Aug
Guan Mai Ning	Herbal Medications	3 tablets TID (7 days)	simvastatin	1.51	25801058	2015 Sep
AZD2327	Depression Treatments	15 mg QD (7 days)	midazolam	1.49	26081137	2015 Nov
resveratrol	Food Products	500 mg QD (10 days)	carbamazepine	1.48	25624269	2015 May
roxithromycin	Antibiotics	300 mg QD (6 days)	midazolam	1.47	7995324	1994
suvorexant	Hypnotics - Sedatives	80 mg QD (14 days)	midazolam	1.47	NDA # 204569	2014
propiverine	Anticholinergics	15 mg BID (7 days)	midazolam	1.46	16183781	2005 Dec
isoniazid	Antibiotics	90 mg BID (4 days)	triazolam	1.46	6140941	1983 Dec
berberine	Herbal Medications	300 mg TID (14 days)	midazolam	1.45	21870106	2012 Feb
oral contraceptives	Oral contraceptives	OC with low doses of estrogen (< 35 ug ethinylestradiol) (> 3 months)	triazolam	1.44	6149030	1984 Nov
delavirdine	NNRTIs	400 mg TID (9 days)	indinavir	1.44	9665503	1998 Jul
daclatasvir	Antivirals	60 mg QD (7 days)	simeprevir	1.44	NDA # 205123	2013
simeprevir	Protease Inhibitors	150 mg QD (11 days)	midazolam	1.43	NDA # 205123	2013
atorvastatin	HMG CoA Reductase Inhibitors (Statins)	10-40 mg/day (chronic treatment)	midazolam IV	1.41	12911366	2003 Sep
tolvaptan	Vasopressin Antagonists	60 mg single dose	lovastatin	1.41	NDA # 022275	2009
almorexant	Hypnotics - Sedatives	200 mg QD (9 days)	midazolam	1.37	22990330	2013 Mar
GSK1292263	Other Antilipemics	300 mg BID (9 days)	simvastatin	1.36	23256625	2013 Jun
evacetrapid	CETP inhibitors	300 mg QD (15 days)	midazolam	1.35	26264702	2015 Dec
linagliptin	Dipeptidyl Peptidase 4 Inhibitors	10 mg QD (6 days)	simvastatin	1.34	20497745	2010 Jun
grazoprevir *(ingredient of Zepatier)*	Antivirals	200 mg QD (7 days)	midazolam	1.34	NDA # 208261	2016
lacidipine	Calcium Channel Blockers	4 mg QD (8 days)	simvastatin	1.33	11259986	2001 Feb
cranberry juice	Food Products	240 mL double strength juice, 1 glass q 15 min x 3	midazolam	1.33	19114462	2009 Mar
pazopanib	Kinase Inhibitors	800 mg QD (17 days)	midazolam	1.32	20881954	2010 Nov
everolimus	Immunosuppressants	10 mg QD (5 days)	midazolam	1.31	23426978	2013 Apr
blueberry juice	Food Products	two doses of 300 mL, separated by 16 hours	buspirone	1.31	22943633	2013 Apr
flibanserin	Central Nervous System Agents	50 mg BID (4 days)	simvastatin	1.31	NDA # 022526	2015
AMD070	Fusion Inhibitors	200 mg BID (8 days)	midazolam	1.29	18362694	2008 Apr

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

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

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

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

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

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

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In Vivo CYP3A Inducers

Inducers	Therapeutic class	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Dose (oral)	PMID or NDA #	Published
Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%))							
rifampin	Antibiotics	budesonide	99.7	36904.5	600 mg QD (7 days)	15726657	2005 Mar
mitotane	Other Antineoplastics	midazolam	94.5	Not Provided	maximum of 3.5 g TID (chronic therapy)	21220434	2011 Apr
avasimibe	Other Antilipemics	midazolam	93.5	Not Provided	750 mg/day (7 days)	12766253	2003 Sep
phenytoin	Anticonvulsants	nisoldipine	89.5	Not Provided	200-450 mg/day (chronic treatment)	8917062	1996 Nov
carbamazepine	Anticonvulsants	quetiapine	86.6	643.1	200 mg TID (26 days)	16390352	2006 Jan
enzalutamide	Antiandrogens	midazolam	85.9	Not Provided	160 mg QD (85±3 days)	NDA # 203415	2012
St John's Wort extract	Herbal Medications	midazolam	80.0	Not Provided	300 mg TID (14 days)	16341856	2006 Jan
rifabutin	Antibiotics	delavirdine	Not Provided	458.0	300 mg QD (14 days)	9224961	1997 Jun
phenobarbital	Anticonvulsants	verapamil	76.6	400.9	100 mg QD (21 days)	3392664	1988 Jul
Moderate Inducers (AUC decreased by 50-80% or CL increased by 2-5 fold (100-400%))							
ritonavir and St. Johns wort	None	midazolam	77.2	Not Provided	ritonavir: 300 mg BID and SJW: 300 mg TID (14 days)	19924124	2010 Feb
semagacestat	Alzheimer's Treatments	midazolam	76.4	324.6	140 mg QD (10 days)	22789530	2012 Oct
efavirenz	NNRTIs	alfentanil	76	369.4	600 mg QD (20 days)	22398970	2012 Apr
tipranavir and ritonavir	Protease Inhibitors	saquinavir	75.6	Not Provided	tipranavir: 500 mg and ritonavir: 200 mg BID (14 days)	18176328	2008 Apr
bosentan	Endothelin Receptor Antagonists	sildenafil	69.0	239.8	62.5-125 mg BID (8 weeks)	15963102	2005 Jul
genistein	Food Products	midazolam	13.7	136.9	1000 mg QD (14 days)	21943317	2012 Feb
thioridazine	Antipsychotics	quetiapine	68.7	104.5	100-300 mg QD (15 days)	22569350	2012 Jun
nafcillin	Antibiotics	nifedipine	62.6	145.1	500 mg 4 times daily (5 days)	12814453	2003 Jun
talviraline	NNRTIs	indinavir	61.7	181.2	500 mg TID (14 days)	10516944	1999 Oct
lopinavir	Protease Inhibitors	amprenavir	59.7	Not Provided	400 mg BID (4 weeks)	15060509	2004 Apr
modafinil	Psychostimulants	triazolam	57.6	35.7	200-400 mg QD (28 days)	11823757	2002 Jan
etravirine	NNRTIs	sildenafil	56.7	Not Provided	800 mg BID (13.5 days)	NDA# 022187	2008
lersivirine	NNRTIs	midazolam	51.4	105.5	1000 mg BID (14 days)	22527351	2012 Nov
Weak Inducers (AUC decreased by 20-50% or CL increased by 20-100% (less than 2 fold))							
eslicarbazepine	Anticonvulsants	simvastatin	49.4	98.4	800 mg QD (14 days)	23726291	2013 Sep
telaprevir	Antivirals	darunavir	48.4	Not Provided	1125 mg BID (4 days)	NDA# 201917	2011
garlic	Food Products	saquinavir	44.7	Not Provided	caplet of GarliPure BID (20 days)	11740713	2002 Jan
bexarotene	Other Antineoplastics	atorvastatin	45.3	Not Provided	400 mg/m2 QD (at least two 4-week cycles)	22057855	2012 Feb
artesunate and mefloquine	Antimalarials	lopinavir	43.1	75.4	4 mg/kg QD artesunate on Days 1-3 + 750 mg mefloquine on Day 1 and 500 m	26452725	2015
amprenavir (fosamprenavir)	Protease Inhibitors	lopinavir	43.0	Not Provided	700 mg BID (2-4 weeks)	15668539	2005 Jan
raltegravir	HIV-Integrase Strand Transfer Inhibitors	darunavir	42.0	Not Provided	400 mg BID	21958880	2012 Feb
lesinurad	Antigout and Uricosuric Agents	amlodipine	41.9	72.5	400 mg QD (24 days)	NDA # 207988	2015
vemurafenib	Kinase Inhibitors	midazolam	39.4	Not Provided	960 mg BID (15 days)	NDA # 202429	2011
troglitazone	Thiazolidinediones	simvastatin	37.7	Not Provided	400 mg QD (24 days)	11361054	2001 May
sorafenib	Kinase Inhibitors	sirolimus	36.9	Not Provided	200 mg BID (11 days)	21045832	2010 Nov
rufinamide	Anticonvulsants	triazolam	36.7	53.4	400 mg BID (11.5 days)	NDA # 021911	2008
sirukumab***	Immunomodulators Biologics	midazolam	35.7	Not Provided	300 mg single dose subcutaneously	26054042	2015 Dec
pleconaril	Antivirals	midazolam	34.6	52.8	400 mg TID (6 days)	16467135	2006 May
ginseng	Herbal Medications	midazolam	34.2	50.7	500 mg BID (28 days)	21646440	2012 Jun
boceprevir	Antivirals	darunavir	34.2	41.0	800 mg every 8 hrs (6 days)	23155151	2013 Mar
sulfinpyrazone	Antigout and Uricosuric Agents	cyclosporine	33.9 (change in C_{avg})		200 mg/day	11124491	2000 Dec
ginkgo	Herbal Medications	midazolam	33.7	52.6	120 mg BID (28 days)	18205997	2008 Feb
vinblastine	Vinca Alkaloids	midazolam IV	33.2	48.8	not provided (4 cycles)	20959500	2010 Nov
nevirapine	NNRTIs	indinavir	32.5	Not Provided	200 mg QD (14 days), then BID (19 days)	10191212	1999 May
armodafinil (R-modafinil)	Psychostimulants	midazolam	32.2	54.7	100-250 mg/day (31 days)	18076219	2008
ticagrelor	Anticoagulants and Antiplatelets	midazolam	31.7	46.5	400 mg QD (6 days)	23870610	2013 Jul
LCL161	Cancer Treatments	midazolam	29.8	34.0	600 mg single dose	23585187	2013 Jun

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In Vivo CYP3A Inducers

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 E. CYP2C19 INHIBITORS AND INDUCERS

Source: University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org. Accessed October 2016 (inhibitors) and March 2015 (inducers). Highlighted rows indicate recent additions to the list.

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In Vivo Inhibitors of CYP2C19 probes

Inhibitor	Therapeutic class	Inhibitor dose (oral)	Substrate (oral)	AUC ratio	PMID or NDA #	Published
POTENT CYP2C19 INHIBITORS (yielding substrate AUCr ≥ 5-fold)						
fluconazole	Antifungals	200 mg QD (4 days)	omeprazole*	13.5	26123704	2016 Jan
fluvoxamine	SSRIs	87.5 mg QD (11 days)	(S)-mephenytoin	9.9	12695344	2003 May
fluoxetine	SSRIs	60 mg QD (14 days, increased from 20 mg on Day 1)	omeprazole*	7.1	24569517	2014 Jun
		20 mg QD (23 days)	moclobemide	2.3~	9585794	1998 Apr
ticlopidine	Anticoagulants and Antiplatelets	200 mg QD (8 days)	omeprazole*	6.2	16272957	2005 Dec
MODERATE CYP2C19 INHIBITORS (yielding substrate AUCr ≥ 2-fold but < 5-fold)						
voriconazole	Antifungals	400 mg BID (1 day) then 200 mg (6 days)	omeprazole*	4.0	Vfend® Product Label	2008
omeprazole	Proton Pump Inhibitors	40 mg QD (8 days)	moclobemide	2.2	11309556	2001 Apr
efavirenz	NNRTIs	400 mg QD (11 days)	proguanil	2.1	19961932	2010 Feb
moclobemide	MAOIs	300 mg single dose	omeprazole*	2.1	11966672	2002 Apr
etravirine	NNRTIs	200 mg BID (14 days)	omeprazole*	2.0	NDA # 022187	2008
WEAK CYP2C19 INHIBITORS (yielding substrate AUCr < 2-fold)						
cimetidine	H-2 Receptor Antagonists	400 mg BID (2 days) and single dose on day 3	proguanil	1.9	10701981	1999 Sep
allicin	Food Products	180 mg QD (14 days)	omeprazole*	1.8	19172254	2009 Jun
tipranavir/ritonavir	Protease Inhibitors	500/200 mg BID (1 day)	omeprazole*	1.8	20147896	2010 Jun
faldaprevir	Antivirals	240 mg BID (14 days)	omeprazole*	1.6	25449227	2015 Apr
armodafinil (R-modafinil)	Psychostimulants	400 mg single dose	omeprazole*	1.4	18076219	2008
simeprevir	Antivirals	150 mg QD (12 days)	omeprazole*	1.3	NDA # 205123	2013
oral contraceptives	Oral Contraceptives	40 µg ethinyl estradiol + 75 µg levonorgestrel/day (10 days)	omeprazole*	1.3	12895199	2003 Aug
clopidogrel	Anticoagulants and Antiplatelets	300 mg QD (1 day) then 75 mg QD (3 days)	omeprazole*	1.3	19398604	2009 May

Probes were selected based on regulatory agency recommendations: (S)-mephenytoin, moclobemide, omeprazole, and proguanil (FDA)
*Omeprazole is also a substrate of CYP3A.
~Fluoxetine is considered as a moderate inhibitor towards moclobemide metabolism.

Other known CYP2C19 inhibitors with no changes in AUC or CL with a CYP2C19 probe available:
chloramphenicol, 5-fluorouracyl, felbamate and oxcarbazepine.

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In Vivo CYP2C19 Inducers

Inducer	Therapeutic Class	Inducer Dose (oral)	Object (oral)	% ↓AUC	% ↑ CL	PMID or NDA #	Published
artemisinin	Antimalarials	250 mg/day (10 days)	(S)-mephenytoin	46.4	85.4	12844133	2003 Jul
carbamazepine	Anticonvulsants	200 mg BID (28 days)	moclobemide	35.3	40.6	19076986	2009 Feb
efavirenz	NNRTIs	600 mg QD (17 days)	omeprazole*	46.4	84.2	22318618	2012 Mar
enzalutamide	Antiandrogens	160 mg QD (85 days)	omeprazole*	70.5	Not Provided	NDA # 203415	2012
ginkgo	Herbal Medications	140 mg BID (13 days)	omeprazole*	40.5	78.6	15608563	2004 Dec
glycyrrhizin	Herbal Medications	150 mg BID (14 days)	omeprazole*	22.8	Not Provided	20350051	2010 Jun
lopinavir and ritonavir	Protease Inhibitors	400/100 mg BID (14 days)	omeprazole*	53% ↓omeprazole metabolic ratio in EMs		16639344	2006 May
st Johns Wort extract	Herbal Medications	300 mg TID (14 days)	omeprazole*	48.9	Not Provided	15001970	2004 Mar
tipranavir and ritonavir	Protease Inhibitors	500/200 mg BID (16 days)	omeprazole*	70.1	Not Provided	20147896	2010 Jun
rifampin	Antibiotic	600 mg/day (7 days)	omeprazole*	89.5	Not Provided	24722393	2014 Sep

* Omeprazole is also metabolized by CYP3A. The extent of induction may also result from induction of minor pathways.

APPENDIX F. 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 G. IWG 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 H. INTERNATIONAL CONSORTIUM PROPOSAL OF UNIFORM RESPONSE CRITERIA FOR MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS (MDS/MPN) 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 CMML) 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 complete blood count. • 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 I. REVISED RESPONSE CRITERIA FOR MYELOFIBROSIS: IWG-MRT AND ELN CONSENSUS REPORT

Response Category	**Required Criteria (for all categories, benefit must last for ≥ 12 weeks to qualify as a response)**
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.

EMH = extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven nonhepatosplenic EMH); LCM = left costal margin; UNL = upper normal limit.

* 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, in the 12 weeks prior to study enrollment, for a hemoglobin level of < 85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any packed red blood cell transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥ 85 g/L.

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

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

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

Source: Tefferi et al 2013.

APPENDIX J. 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.

CR = complete response; FLC = free light chain; PR = partial response; SD = stable disease; sCR = stringent complete response; VGPR = very good partial response.

Note: 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.

[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.

[3] For progressive disease, serum M-component increases of ≥1 gm/dl are sufficient to define relapse if starting M-component is ≥ 5 g/dl.

[4] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

Source: Durie et al 2006.

APPENDIX K. CRITERIA FOR EVALUATING DISEASE RESPONSE AND PROGRESSION IN SUBJECTS WITH MULTIPLE MYELOMA TREATED BY HIGH-DOSE THERAPY AND HAEMOPOIETIC STEM CELL 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 L. 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.