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Protocol Page

Phase II Study of INCB018424 in Patients with Advanced Hematologic Malignancies 2007-0925

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Study Chair:	Farhad Ravandi-Kashani
Additional Contact:	Kwann C. Vigilant Maria E. Diaz-Pines-Mateo Leukemia Protocol Review Group
Department:	Leukemia
Phone:	713-745-0394
Unit:	428
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TITLE: PHASE II STUDY OF INCB018424 IN PATIENTS WITH ADVANCED HEMATOLOGIC MALIGNANCIES

Protocol No:

Principal Investigator:

Farhad Ravandi-Kashani, M.D.

Co-Principal Investigator:

Jorge Eduardo Cortes, M.D.
Hagop M. Kantarjian, M.D.

Co-Investigators:

Srdan Verstovsek, M.D., Ph.D.
Stefan Faderl, M.D.
Guillermo Garcia-Manero, M.D.
Gautham Borthakur, M.D.
Jan A. Burger, M.D., Ph.D.
Susan M. O'Brien, M.D.
Charles A. Koller, M.D.
Alessandra Ferrajoli, M.D.
Marina Konopleva, M.D., Ph.D.
William G. Wierda, M.D., Ph.D.
Deborah Ann Thomas, M.D.
Zeev Estrov, M.D.
Xuelin Huang, M.D., Ph.D.

TABLE OF CONTENTS

Page

1. Objectives 3

2. Background 3
2.1 Diseases to be studied 3
2.2 INCB018424 Phosphate 3
2.3 Rationale 5

3. Patient eligibility 7
3.1 Inclusion criteria 7
3.2 Exclusion criteria 8

4. Treatment plan 9
4.1 Dose of INCB018424 and Treatment Cycle 9
4.2 Administration of INCB018424 11
4.3 Supportive Care Guidelines 11
4.4 Duration of Therapy 12
4.5 Dosing Delays/Dosing Modifications 12
4.6 Concomitant medications 13

5. Study procedures 13
5.1 Screening 13
5.2 Study Procedures 15

6. Response definitions 22

7. Pharmacokinetic and Pharmacodynamic Methods 25
7.1 Pharmacokinetic Methods 25
7.2 Pharmacodynamic Methods 25
7.3 Bone Marrow Aspiration, Biopsy and Cytogenetics 26

8. Regulatory and Reporting Requirements 27
8.1 Expedited Adverse Event Reporting 29

9. Statistics 29
9.1 Study Population 29
9.2 Efficacy and PK/PD Variables 30
9.3 Safety Analysis 31
9.4 Study Definitions 31
9.5 Reporting and Exclusions 32

10. **Ethics** 33
10.1 Institutional Review Board 33
10.2 Informed Consent 33
References 36

1. OBJECTIVES

This study is a phase II study of the JAK kinase inhibitor INCB018424 phosphate in patients with advanced hematological malignancies who have failed prior therapy. The objectives of the proposed study are:

Primary:

To observe the anti-tumor effects of INCB018424 in patients with relapsed/refractory AML, ALL, and MDS (including CMML), and blast phase or tyrosine kinase refractory CML.

Secondary:

1. To determine the safety and tolerability in patients with relapsed/refractory AML, ALL, and MDS (including CMML), and blast phase or tyrosine kinase refractory CML.

2. To determine the pharmacokinetics and preliminary pharmacodynamic activity including the modulation of signal transducer and activator of transcription (STAT) protein phosphorylation.

2. BACKGROUND

2.1 Diseases to be studied

Despite progress in leukemia therapy, most adult patients with leukemia still die from disease progression, and improvements in therapy are still required for pediatric patients with resistant or relapsed leukemia. For patients with acute myeloid leukemia (AML) who fail to achieve a complete remission (CR) with first attempts at induction or who have relapsed disease, current therapy is inadequate with a true long term cure rate of less than 10% and therefore, new agents are needed.[1] Adult patients with acute lymphocytic leukemia (ALL) who fail to achieve a CR with first attempts at induction or who have relapsed disease have a true long term cure rate of less than 10%.[2] Patients with chronic myelogenous leukemia (CML) who enter blastic phase having received prior imatinib therapy or who fail imatinib therapy for blastic phase have a median survival of 3 to 9 months with current therapies.[3] Similarly, patients with CML who have failed two or three tyrosine kinase inhibitors have few alternative options.

2.2 INCB018424 Phosphate

2.2.1 Drug Product

INCB018424 phosphate is an inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs) that is currently being developed for treatment of myeloproliferative disorders under IND No. 77,456. Unless otherwise

noted, INCB018424 phosphate is referred to throughout this IND as INCB018424. INCB018424 Phosphate Tablets 5 and 25 mg (free base equivalent), as disclosed in IND No. 77,456, will be used in the proposed studies described in this IND. Additional details of the CMC characterization of INCB018424 may be found in the Clinical Investigators Brochure (CIB).

IND No. 77,455 was submitted to the FDA Division of Anesthesia, Analgesic, and Rheumatology Products to develop INCB018424 Phosphate Capsules for the treatment of patients with rheumatoid arthritis. Phase 1 of this study (Study INCB 18424-132) has safely completed the short term (10 day) dosing of normal volunteers with the 25 mg BID doses of INCB018424 that are proposed to be used in this study.

2.2.2 *In Vitro* Pharmacology of INCB018424

INCB018424 is a potent inhibitor of all JAK family members (IC_{50} values < 5 nM), with modest selectivity for JAK2. It does not significantly inhibit a broad panel of 26 other kinases when tested at concentrations approximately 100 fold higher than its potency against the various JAKs. Moreover, in cell-based assays relevant to the pathogenesis of MPDs and cancer, such as cytokine-induced JAK-STAT signaling, cytokine-driven tumor cell proliferation as well as growth of a cell line expressing the JAK2V617F mutation, INCB018424 demonstrates excellent potency (IC_{50} values of ~ 80-150 nM). This effect is not due to general cytotoxicity, because INCB018424 (up to 20 μM) had no significant effect on the growth of cytokine-independent cell lines. In addition, INCB018424 inhibits cytokine-induced JAK/STAT phosphorylation in human whole blood with an IC_{50} value of ~ 300 nM, providing a useful biomarker of INCB018424 pharmacological activity. Additional details as to the *in vitro* pharmacology of INCB018424 may be found in the Clinical Investigators Brochure (CIB).

2.2.3 *In Vivo* Pharmacology of INCB018424

Treatment of mice with orally administered INCB018424 resulted in a dose-dependent suppression of STAT3 phosphorylation and tumor growth in the cytokine-dependent multiple myeloma INA-6 xenograft model at doses ≥ 10 mg/kg BID. Moreover, oral administration of INCB018424 inhibited JAK pathway signaling, tumor cell growth and splenomegaly in mice resulting from intravenous inoculation of a BaF3 cell line engineered to express JAK2V617F (BaF3-JAK2V617F). Additional details as to the *in vivo* pharmacology of INCB018424 may be found in the Clinical Investigator's Brochure (CIB).

Pharmacological data obtained in both *in vitro* and *in vivo* model systems support the potential utility of orally administered INCB018424 in the treatment of JAK-dependent hematological malignancies.

INCB018424 has been administered orally in single doses to healthy subjects in ongoing study INCB 18424-131. In study INCB 18424-131, single oral doses of 5 mg, 10 mg, 25 mg, 50 mg, 100 mg and 200 mg have been administered with monitoring of adverse events, clinical laboratories, PK and pharmacodynamic parameters. All single doses were well tolerated with no observed drug-associated adverse events. The pharmacodynamic preliminary, unaudited draft data available indicate that single doses of INCB018424 are able to inhibit interleukin-6 induced STAT3 phosphorylation in a dose dependent manner. The 200 mg dose of 18424 produced ~80-95% inhibition of STAT3 phosphorylation between 1-8 hours following dosing with levels returning to baseline by 48 hours.

In study INCB 18424-132, multiple oral doses of 25 mg BID and 50 mg daily and BID have been administered with monitoring of adverse events, clinical laboratories, PK and pharmacodynamic parameters. The preliminary unaudited pharmacodynamic draft data available indicate that multiple doses of INCB018424 are able to inhibit interleukin-6 induced STAT3 phosphorylation in a dose dependent manner, similar to data obtained in the single dose studies. The data on day 1 and day 10 demonstrated similar levels of inhibition of STAT3 phosphorylation, indicating a lack of cumulative biological activity. From an evaluation of the safety data obtained in this study, the preliminary conclusion is that the INCB018424 50 mg BID dose is considered too high for healthy volunteers and patients without serious diseases. Dosing in these populations should be limited to 25 mg BID or lower and up to 50 mg daily, although higher doses than 50 daily may be safe but have not been tested beyond single doses. However, in patients with malignancies dose escalation could continue until the maximum tolerated dose is achieved due to the different benefit-risk ratio in these subjects and because these patients may respond differently.

Under IND No. 77,456, INCB018424 has also been dosed to three patients with multiple metaplasia with myelofibrosis at 25 mg BID for over five months with clinical benefit but without notable toxicity. In this study four patients have also been dosed at 50 mg INCB018424 BID but, according to protocol, dosing was halted after two of four subjects presented with significant reductions in peripheral blood neutrophils and platelets. Subsequently, according to protocol, three additional patients have been treated at the 25 mg BID dose for at least 1 month to establish this dose as the MTD in this population.

2.3 Rationale

The Jak family of kinases comprises four proteins (Jak1, Jak2, Jak3, and Tyk2) that can associate with cytokine receptor subunits, phosphorylate them, and in doing so create docking sites on the receptors for binding of

SH2-containing proteins. In general, Jaks consist of several domains (JH1-JH7), including a tyrosine kinase domain, and the functional significance of these domains has been characterized by mutational analysis. Jaks are able to associate with the cytokine receptors as well as with each other. Dimerization/oligomerization of cytokine receptor subunits as a result of ligand binding leads to juxtaposition of Jaks. This results in transphosphorylation and activation of their kinase activity and the phosphorylation of downstream signaling proteins such as Stats, *Src*-kinases, and adaptors such as Shc, Grb2, and Cbl.[4]

Abnormalities of Jak function have been associated with a number of disorders. For example, chromosomal translocations resulting in TEL-JAK2 constructs lead to the constitutive activation of STAT5, IL-3-independent cellular proliferation, and leukemogenesis. The translocation t(9;12)(p24;p13) results in the fusion of the kinase catalytic region of JAK2 with the transcription factor TEL generating the constitutively active TEL-JAK2. Similarly, infection with oncogenic viruses such as human T-cell lymphotrophic virus, type I, and Abelson murine leukemia viruses results in enhanced kinase activity of Jaks, possibly accounting for their leukemogenic potential.

The STAT transcription factors are coded by six known mammalian genes and include 10 different STAT proteins including different isomers of STATs 1, 3, 4, and 5. Like other transcription factors STATs have a well-defined structure including a DNA-binding domain, a conserved NH_2-terminal domain, a COOH-terminal transactivation domain, and SH2 and SH3 domains. Their activation through tyrosine phosphorylation results in their dimerization and translocation into the nucleus where they activate specific genes.[4]

Jak proteins activate a number of intracellular signaling proteins, among which STATs are the best defined. Binding of a cytokine to its receptor rapidly induces tyrosine phosphorylation of the cytoplasmic domains of the receptor by activated Jak kinases, thus providing a docking site for STAT proteins, which are then phosphorylated. This phosphorylation of STATs leads to their homo- or heterodimerization and translocation to the nucleus, followed by DNA binding and gene activation. The specificity for STAT phosphorylation is determined by the receptor docking sites and not the Jak kinases. Also, different STAT proteins have different DNA-binding affinities, resulting in activation of specific genes. STATs also interact with other transcription factors such as the p300/cyclic AMP-responsive element binding protein family of coactivators to activate genes. The transcriptional activity of STATs may also be regulated by the phosphorylation of their serine and threonine residues, although the implications of such regulation are not known.

STATs mediate diverse and sometimes opposite cellular events affecting growth, differentiation, and apoptosis. For example, STATs can mediate both growth arrest and cellular proliferation. Specifically, STAT1 mediates the growth-inhibitory effects of IFN-γ, through the induction of the CDKI $p21^{waf1}$, whereas STAT5 mediates proliferative effects of IL-3 and GM-CSF. Similarly, phosphorylation of STAT3 can result both in IL-6- and IL-10-induced growth arrest, and in GM-CSF- and IL-3-induced proliferation. STATs also modulate cellular differentiation and apoptosis. Reconstitution of STAT1 in STAT1-null U3A cells (which do not respond to TNF-α) restores basal caspase expression and renders them sensitive to TNF-induced apoptosis. Conversely, STAT3 and STAT5 mediate the antiapoptotic effects of IL-6 and IL-2, respectively. STAT1 activates the caspase cascade through up-regulation of Fas and FasL expression in response to IFN-γ. The exact mechanisms underlying these diverse effects are being elucidated.[4]

Abnormalities of the JAK-STAT pathways have been described in a variety of leukemias and their inhibition can be a goal for leukemia therapy.

3. PATIENT ELIGIBILITY

Patients in this trial can be of any race and either gender.

3.1 Inclusion Criteria

A. Must be at least 18 years of age.

B. Patients must have relapsed/refractory leukemias for which no standard therapies exist. Patients with poor-risk myelodysplasia (MDS) [i.e. refractory anemia with excess blasts (RAEB-1 or RAEB-2) by WHO classification] and chronic myelomonocytic leukemia (CMML) who failed prior therapy are also candidates for this protocol. Relapsed/refractory leukemias include acute non-lymphocytic leukemia (AML) by WHO classification (i.e. ≥ 20% blasts), acute lymphocytic leukemia (ALL), or chronic myelogenous leukemia (CML) in blast crisis. Patients with CML who are resistant to at least two tyrosine kinase inhibitors and have no standard stem cell transplant option are also eligible.

C. ECOG performance status of 0-2.

D. A female of childbearing potential must have a negative serum or urine pregnancy test at screening. Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must use acceptable contraceptive methods (abstinence, intrauterine device [IUD], oral contraceptive or double barrier device), and must have a negative serum or urine pregnancy test within 2 weeks prior to beginning treatment on this trial. Sexually active men must also use acceptable contraceptive methods for the duration of time on study.

E. Must be able and willing to give written informed consent.

F. In the absence of rapidly progressing disease, the interval from prior treatment to time of study drug administration should be at least 2 weeks for cytotoxic agents, or at least one week for noncytotoxic agents. Persistent clinically significant toxicities from prior chemotherapy must not be greater than grade 2.

G. Patients must have the following clinical laboratory values unless considered due to leukemic organ involvement:
    1. Serum creatinine ≤ 2.0 mg/dl.
    2. Total bilirubin ≤ 1.5x the upper limit of normal unless considered due to Gilbert's syndrome or hemolysis.
    3. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 2.5x the upper limit of normal unless considered due to organ leukemic involvement (then ≤ 5x the upper limit of normal).

H. Patients with active CNS disease are included and will be treated concurrently with intrathecal therapy. INCB018424 will not be administered by intrathecal route.

3.2 Exclusion Criteria

Patients with any one of the following criteria will not be eligible for study participation:

A. Uncontrolled intercurrent illness including, but not limited to uncontrolled infection, symptomatic congestive heart failure, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

B. Active heart disease including myocardial infarction within the previous 3 months, symptomatic coronary artery disease, arrhythmias not controlled by medication, or uncontrolled congestive heart failure.

C. Current treatment or treatment within 2 weeks or 5 half-lives (whichever is longer) prior to the first dose of study medication with another investigational medication or current enrollment in another investigational drug protocol (unless there is evidence of rapidly progressive disease in which case a shorter interval from last therapy may be acceptable).

D. Females who are pregnant or are currently breastfeeding.

E. Patients receiving therapy with intermediate or high dose steroids greater than the equivalent of 10 mg prednisone per day are not allowed.

F. Evidence of active hepatitis or human immunodeficiency virus (HIV) infection determined by screening laboratory test results or results within prior 3 months.

G. Any unresolved toxicity equal to or greater than Grade 2 from previous anticancer therapy, except for stable chronic toxicities not expected to resolve, such as peripheral neurotoxicity.

H. Incomplete recovery from any prior surgical procedures or had surgery within 4 weeks prior to study entry, excluding the placement of vascular access.

I. Uncontrolled intercurrent illness or any concurrent condition that, in the Investigator's opinion, would jeopardize the safety of the patient or compliance with the protocol.

J. In patients who are receiving medications known to be inhibitors or inducers of CYP3A4 every effort will be made to change these medications to acceptable alternatives. If this is not safely possible, patients will be excluded from participation in the study. If a patient is already on the study, must be started on a CYP3A4 inhibitor, and is demonstrating benefit from the study, they will be seen twice weekly in the first cycle and weekly in the subsequent cycles for toxicity evaluation and their dose will be modified according to the table in section 4.5 in the event of a toxicity thought to be related to the study drug. A list of CYP3A4 inducers and inhibitors is provided in Appendix I.

4. TREATMENT PLAN

4.1 Dose of INCB018424 and Treatment Cycle

This is a phase II study of oral INCB018424 in patients with relapsed/refractory AML, ALL, and MDS (including CMML), and blast phase or tyrosine kinase refractory CML. The starting dose of INCB018424 will be 25 mg po twice daily, which has been determined to be the maximum tolerated dose in patients with myelofibrosis with myeloid metaplasia and a dose that is tolerated for ten days in normal human volunteers.

INCB018424 will be administered orally at a dose of 25 mg BID for 7 days each week for 4 weeks (cycle number 1). Patients will be evaluated after 1 full cycle of therapy (28 days) for response. Responding patients or patients with stable disease will be allowed to continue on study at a dose of 25 mg INCB018424 BID until progression. The response assessment for the purpose of study statistical evaluation will be after two cycles (8 weeks) of therapy. Patients with progressive disease, based on clinical and laboratory evaluation, will, at the discretion of the Investigator, either be removed from the study or, as long as the 25 mg BID dose has been well tolerated, dose escalated to 50 mg INCB018424 BID. In instances of dose escalation to 50mg BID, patients will be evaluated after

1 full cycle of therapy (28 days) for response and toxicity. At that point, patients with continued progressive disease, based on clinical and laboratory evaluation, will be removed from the study. In instances of dose escalation, the response assessment for the purpose of study statistical evaluation will be after two cycles (8 weeks) of therapy at the 50 mg BID dose.

Patients with chronic phase CML who have failed at least 2 prior tyrosine kinase inhibitors and do not have a standard transplant option will be assessed for response after 3 months of therapy in the absence of loss of disease control and they may continue therapy if they demonstrate any clinical benefit. Patients with chronic phase CML will not be allowed to have the dose escalation as this population has less of a life-threatening disease situation.

Patients who, in the opinion of the Investigator, are demonstrating cytopenias not thought to be related to disease progression and who may be receiving benefit from treatment may, at the discretion of the Investigator, be dose adjusted to a lower dose of INCB018424 BID or an equivalent dose given daily (see section on dose modifications below). Studies in subjects with myelofibrosis with myeloid metaplasia using different doses and schedules of INCB18424 may be used as a guide to dose adjustments in this study.

Patients will initiate the first cycle of therapy at MDACC. They will have weekly visits at their local physician's office with physical exam and review of symptoms during cycle one. In the absence of intolerable side effects, patients may return to the local oncologist for laboratory tests, but only MDACC investigators can make treatment decisions. Patients will return to MDACC every 4 weeks to be evaluated and receive their new supply of study medication. For the second and third cycle, patients will return to MDACC every 4 weeks to be evaluated and receive their new supply of study medication. Subsequently, patients will return to MDACC every three months. Because of drug stability issues, some patients may have to continue to be seen on a monthly basis to have the drug provided.

For toxicity evaluation, patients enrolled in the study will be considered in 2 cohorts (I) those with relapsed/refractory AML, ALL, and MDS (including CMML), and blast phase CML, and (II) those with chronic phase CML. At any time after 6 patients are enrolled in cohort I (including AML, ALL, MDS, blast phase CML patients), if 30% or more patients experience grade 3 or 4 toxicity thought to be directly related to INCB018424 and lasting longer than 2 weeks, then we will stop that cohort of the trial. At any time after 6 patients are enrolled in cohort II (including chronic phase CML patients), if 15% or more patients experience grade 3 or 4 toxicity thought to be directly related to INCB018424 and lasting longer than 2 weeks, then we will stop that cohort of the trial.

4.2 Administration of INCB018424

This is an open label, non-randomized, study of INCB018424, administered orally to patients with relapsed/refractory AML, ALL, and MDS (including CMML), and blast phase or tyrosine kinase refractory CML. The study of INCB018424 in each disease listed will be conducted in two parts. The first part is intended to enroll a maximum of 10 patients within each of the four disease categories included in this study and to identify whether significant benefit is observed. If a minimum of one patient shows benefit that is considered significant, there will be an expanded cohort of 20 additional patients treated in that arm of the study.

Patients will receive 50 mg/day administered orally in two divided doses (i.e., BID: every 12 hours $\pm$ 2 hours). Within each arm of the study, three patients will be initially treated and observed for toxicity for one treatment cycle (28 days) before the additional seven patients are entered. Dose reduction will be considered if the number of patients experiencing grade 3 or higher toxicities exceed 2/3, 3/4, 4/7, 5/10, 6/14, 7/18, 8/22, 9/26. Treatment will be administered primarily on an outpatient basis, but can be administered as an inpatient if the patient is hospitalized for other reasons.

The 5 mg tablets have been shown to be stable when stored up to one month at 25ºC/60%RH and 40ºC/75%RH; the 25 mg tablets have been shown to be stable when stored for three months at 25º/60%RH and 40º/75%RH. (25ºC = 77ºF, 40ºC = 104ºF).

4.3 Supportive Care Guidelines

Supportive measures including erythropoietin, analgesics, blood transfusions, antimicrobials, and hematopoietic colony stimulating factors for treatment of cytopenias are permitted.

Prophylactic use of hematopoietic colony stimulating factors is not permitted.

Other chemotherapy, investigational cytotoxic agents, radiation, or biologic therapy is prohibited while the patient is on study with the following exceptions during cycle 1: During the first 7 days of study only, patients may receive leukaphereses (not more than three procedures per week and not more than five procedures in total to control elevated blast and/or platelet counts and/or hydroxyurea (up to a maximum of 5 gm/day) for a maximum of 14 days. Intrathecal chemotherapy to treat isolated CNS involvement of leukemia is allowable.

4.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Lack of objective response after 2 cycles of therapy (3 cycles if there is dose escalation to 50 mg BID after cycle 1) unless INCB018424 is considered to be of clinical benefit to the patient
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.5 Dosing Delays/Dose Modifications

Dose Adjustments

The dose of INCB018424 will be adjusted according to the guidelines shown in the following tables for INCB018424 - related clinically significant toxicity. If a toxicity is not covered in the table, doses may be reduced or held at the discretion of the investigator for the patient's safety. Dose adjustments for hematological toxicity are based on the blood counts obtained in preparation for the day of treatment i.e. CBC within 3 days of Day 1 of that cycle.

Patients will be withdrawn from the study if they fail to recover to CTC AE grade 0 to 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related toxicity within 2 weeks (leading to treatment delay of > 2 weeks) unless the investigator feels that the patient should remain in the study because of evidence that the patient is/may continue deriving benefit from continuing study treatment.

Patients with toxicities that are manageable with supportive therapy may not require dose reductions. Patients requiring greater than 1 dose reduction of INCB018424 should be withdrawn from the study, unless INCB018424 is considered to be of clinical benefit to the patient.

Dose modification for neutropenia and thrombocytopenia grade 4 persisting beyond 2 weeks of therapy is allowed if the treating physician believes them to be related to the treatment and not the underlying disease. The dose can be held until the AE is to grade 2 or lower; then INCB018424 will be restarted at 15 mg BID or an equivalent dose given daily. Alternatively, at the discretion

of the treating physician, the dose may be reduced to 15 mg BID without holding the drug if the treating physician believes that the cytopenia is related to a combined effect of the drug and uncontrolled disease.

Dosing for INCB018424- Related Toxicities

NCI CTC AE **Grade**	**INCB018424**
Grade 0-2 non-hematological toxicity	No dose reduction. Grade 2 toxicities that are persistent and intolerable (e.g. stomatitis) can result in dose delays or dose reduction to 15 mg BID in Cycle 2 or beyond.
Grade 3-4 clinically significant non-hematological toxicity	Hold until recover to NCI CTC AE grade 0-2 If recovery occurs within 2 weeks after treatment has been held, dose should be reduced to 10 mg or 15 mg BID. At the discretion of the investigator and if the patient is considered to be benefiting, the patient will receive an intermittent dose schedule, alternating treatment periods and recovery periods at the 25 mg BID dose. i.e alterations to the dose and schedule that is thought to be beneficial to the patient in the responding patients may be allowed after discussion with IRB, FDA and the PI.

4.6 Concomitant medications

INCB018424 is predominantly metabolized by CYP3A4.
The potential for INCB018124 to inhibit or induce human Cytochrome P450 enzymes has been extensively investigated. The available data suggests that the potential for INCB018124 to cause clinical drug interaction via CYP inhibition is low. Furthermore, in vitro data suggest that the potential for INCB018124 to induce CYP3A4 is also low. Therefore there is little potential to interact with other drugs.

5. STUDY PROCEDURES

5.1 Screening

The following procedures are performed during screening, staging and workup (Table 5.1, below). These procedures are to be performed within 4 weeks prior to study drug administration, except where indicated.

Table 5.1: Procedures During Screening, Staging and Workup

Procedures	Specifics
Informed consent	
Full History and Physical Examination	History – present illness, all surgeries, all other medical illnesses, review of systems, allergies, all prior therapy for cancer and concurrent meds; F Physical exam – record weight, and note abnormalities in any major organ system (including but not limited to neurologic, head and neck, lymph nodes, cardiovascular, pulmonary, abdomen, extremities), note and measure sites of disease
Vital signs (including temperature, pulse, and blood pressure)	
ECOG performance status	
Pregnancy test (females of child-bearing potential only)	At screening, within 2 weeks prior to first dose
Disease status (note: measurement of lesions assessed only by physical exam should be performed within 1 week prior to first dose) Note: Bone marrow biopsy or aspirate within 4 weeks prior to first dose of drug in all patients. *Cytogenetics, immunohistochemistry, and histochemistries performed as indicated.*	Staging with bone marrow biopsy or aspirates. Lumbar punctures or radiographic investigations as appropriate to the disease.
Serum chemistries (repeat if screening chemistries completed greater than 72 hours prior to the first dose)	Sodium, potassium, chloride, CO_2, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, AST and ALT, total bilirubin, alkaline phosphatase, total protein, albumin, uric acid, lactic dehydrogenase
Urinalysis (including microscopic)	
CBC with platelets (repeat if screening test completed greater than 24 hours prior to the first dose)	
PT/aPTT	
Chest X-ray PA-LAT	
HIV, Hepatitis B and C	Results of test performed within past 3 months acceptable

PA-LAT = Posterior anterior - lateral.

5.2 Study Procedures

	Screening Phase	Treatment Phase										End of Treatment
		Cycle 1				Cycle 2+3				Subsequent Visits - For details see Footnotes		
Visit	**Day -28 to Day -1**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 15**	**End of Study[o]**
Evaluation – All evaluations have a +/- 2 day window except for bone marrow biopsy (see footnote i).												
Informed consent[a] / Eligibility criteria	X	X										
Medical & medication history[b]	X	X	X	X	X	X				X[b]		X
Physical examination[c]	X	X	X	X	X	X				X[c]		X
Vital signs[c]	X	X	X	X	X	X				X[c]		X
Overall Response assessment (IWG-MRT)[d]						X				X[d]		X
ECOG performance status[e]	X					X				X[e]		X
Concomitant medication review[f]		X	X	X	X	X				X[f]		X
Clinical laboratory tests[g]	X		X	X	X	X		X		X[g]		X
CBC[h]	X		X	X	X	X	X	X	X	X[h]	X[h]	X
PT/PTT	X											
CXR	X											
Pregnancy test[g]	X											
FSH test[g]	X											
Serology / HIV laboratory tests[g]	X											
Urinalysis[g]	X											
BM aspiration, biopsy and cytogenetics[i]	X									X[i]		
Administer 1st dose of INCB018424[j]		X										
Dispense INCB018424 study medication[j]		X				X				X[j]		
PK sampling [k]		X				X						
PD biomarker sampling [l]		X				X				X[l]		X
Adverse event / Intercurrent illness assessment[m]		X	X	X	X	X				X[m]		X
Study medication compliance[n]			X	X	X	X				X[n]		X

a. Informed consent must be obtained at Screening. At Screening and Day 1, assess eligibility for study entry and review eligibility for study entry on Day 1.
b. Medical history will be done at each visit. Medication history will be obtained only at the screening visit.
c. A complete examination will be performed at Screening and the End-of-Study Visit . A “targeted” examination will be performed at all other visits. During the treatment phase, weekly visits at the local physician’s office are required during 1st cycle of therapy with a review of constitutional symptoms and physical exam, including transfusion requirement. During 2nd and 3rd cycles visits are every 4 weeks, and then every 3 months thereafter. All examinations will include body weight. On Day 1 of Cycle 1, before PK/PD blood-draws, the vital signs will be done as well as with the physical exams. On all other clinical visits vital signs are taken once. Overall response assessments will be graded according to consensus criteria for treatment response.

d. Overall response assessments are required on Day 1 of Cycles 2, 3, and 4 and then every 3 months thereafter. If the dose of INCB018424 is escalated to 50 mg BID after cycle 1, then overall response assessments are required on Day 1 of Cycles 3, 4, and 5 and then every 3 months thereafter.
e. ECOG performance criteria must be 0, 1 or 2 at screening. ECOG assessment is required on Day 1 of 2nd and 3rd cycles and thereafter every scheduled subsequent visit on Day 1.
f. All medications received within 30 days prior to the Screening Visit are to be recorded. Reassessments will be done weekly at the local physician's office during 1st cycle of therapy and then every 4 weeks during 2nd and 3rd cycles and thereafter every 3 months during scheduled visits.
g. Serum chemistry (Sodium, potassium, chloride, CO_2, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, AST or ALT, total bilirubin, alkaline phosphatase, total protein, albumin, uric acid, lactic dehydrogenase) is required every week during the 1st cycle and every two weeks during Cycles 2 and 3, and at each scheduled subsequent visit. Urinalysis is required only at screening and at the end of study visit. Hepatitis serology and HIV laboratory test will be performed only during the Screening Visit if there are no results available from past 3 months. A pregnancy test will be obtained at screening. Urine pregnancy test will then be performed if there is a suspicion of pregnancy. A serum pregnancy test will be performed to confirm positive results obtained from a urine test. FSH test will only be performed on females who have been amenorrheic for >1 year, and if levels are elevated no further pregnancy testing is required for these female patients.
h. Complete blood count (CBC) including absolute neutrophil count and platelet count are required weekly for Cycle 1, 2 and 3 and every two weeks for subsequent visits.
i. Bone marrow aspiration or biopsy will be taken during the screening phase (within 4 weeks of starting drug), and at start of Cycle 4 (± 7 days), Cycle 7 (± 7 days), and thereafter at start of each 6^{th} subsequent cycle (+/- 7days). Evaluation will include staining for fibrosis and cytogenetics if abnormal prior to therapy. Cytogenetic studies will be repeated only in patients with abnormalities at baseline, on Day 1 of Cycles 4 and 7 and thereafter on Day 1 of each 6^{th} subsequent cycle(+/-7days). If unable to obtain BM aspirate, cytogenetics may also be done on peripheral blood collected for PD/PK analysis.
j. Instruct patient that the dose is to be taken at 12 hour intervals at approximately the same time each day. The first dose of each day should be taken in the morning.
k. For Cycle 1, PK samples to be collected on Day 1 at pre-dose, 0.5, 1, 1.5, 2, 4, 6, and if possible 8 hours after administration of the morning dose of INCB018424. For Cycles 2 and 3, a PK sample will be collected at pre-dose on Day 1.
l. For Cycle 1, plasma and whole blood PD samples will be collected on Day 1 at pre-dose and 2, hours after administration of the morning dose of INCB018424. For Cycles 2, 3, and each subsequent scheduled visit to MDACC, plasma and whole blood PD samples will be collected at pre-dose on Day 1. Final PD sample will be collected at End-Of–Study visit. Not all samples may be collected on all patients. See Appendix F.
m. Adverse events (AEs) considered related to study medication must be followed until resolution, start of a different treatment therapy or no longer considered to be clinically relevant in the opinion of the investigator. During the treatment phase, AE assessment is required weekly at the local physician's office during 1st cycle of therapy. During the 2nd and 3rd cycles assessments are required every 4 weeks, and then every visit thereafter.
n. Compliance should be checked at each scheduled clinical visit. Any unused drug in sealed bottles will be returned to Incyte or its designee. MDACC will follow internal procedures to destroy and dispose of unused drug in open/unsealed bottles.

o. End-of-Study procedures are to be completed if patient completes study or at anytime patient terminates treatment early in the study.

5.2.1 Cycle 1

5.2.1.1 Cycle 1 - Day 1

Patients who meet all of the study entrance criteria and none of the exclusion criteria will return to the study site on Day 1. The following procedures will be performed:

- Review of eligibility criteria including laboratory results.
- Review of prior/concomitant medications.
- Targeted physical examination.
- Record vital signs.
- Intercurrent illness will be assessed pre-dose.
- Administration of the 1st dose of the INCB018424.
- Blood samples for plasma PK assessment will be drawn pre and post-dose with exact time recorded as defined in the Study calendar. PK samples to be collected on Day 1 at pre-dose, 0.5, 1, 1.5, 2, 4, 6, and if possible 8 hours after administration of the morning dose of INCB018424. If not feasible, all samples do not have to be drawn in all patients.
- Blood sample for plasma and whole blood PD will be collected pre-dose, and 2 hours after administration of the morning dose of INCB018424.
- Adverse events will be assessed post-dose.
- Study medication for the first Cycle will be dispensed and the Study staff will instruct the patient regarding dosing regimen.
- Patients will be instructed to call the Investigator or designated research staff if they experience any “troubling” signs and/or symptoms that are of moderate or greater severity.
- Patients will be asked to return to the clinical site on Day 8. Patients will be asked to bring the study medication.

5.2.1.2 Days 2 to 7

Patients will self-administer study medication as instructed twice daily at approximately 12 hour intervals in an out-patient setting.

5.2.1.3 Day 8 ± 2

The following procedures will be performed:

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical examination and vital signs.
- Blood sampling for blood serum chemistry tests, CBC with Differential, ANC, platelet count
- Review all safety information and criteria for dosing interruptions to determine if patients should receive further doses.

- Patients will be instructed to call the Investigator or designated research staff if they experience any “troubling” signs and/or symptoms that are of moderate or greater severity.
- Patients will be asked to return to the clinical site on Day 15.

5.2.1.4 Days 9 to 14

Patients will self-administer study medication as instructed twice daily at approximately 12 hour intervals in an out-patient setting.

5.2.1.5 Day 15 ± 2

The following procedures will be performed:

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical examination and vital signs.
- Blood sampling for blood serum chemistry tests, CBC with Differential, ANC, platelet count
- Patients will be instructed to call the Investigator or designated research staff if they experience any “troubling” signs and/or symptoms that are of moderate or greater severity.
- Patients will be asked to return to the clinic on Day 22.
- Review all safety information and criteria for dosing interruptions (Section 10.4) to determine if patients should receive further doses.

5.2.1.6 Days 16 to 21

Patients will continue to self-administer study medication per instructions twice daily at approximately 12 hour intervals in an out-patient setting.

5.2.1.7 Day 22 ± 2

The following procedures will be performed:

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical examination and vital signs.
- Blood sampling for the blood serum chemistry tests, CBC with Differential, ANC, platelet count
- Patients will be instructed to call the Investigator or designated research staff if they experience any “troubling” signs and/or symptoms that are of moderate or greater severity.
- Patients will be asked to return to the clinic on Day 1 of Cycle 2 (Day 28 to 31 of Cycle 1). Patients will be asked to bring all study medication with them to the visit.

- Due to PK and PD samples being collected at the next visit, patients will be asked to withhold their morning dose of study medication on Day 1 of Cycle 2.
- Review all safety information and criteria for dosing interruptions (Section 10.4) to determine if patients should receive further doses.

5.2.1.8 Days 23 to 27

Patients will continue self-administering study medication per instructions twice daily at approximately 12 hour intervals in an out-patient setting.

5.2.2 Cycles 2 and 3

5.2.2.1 Day 1 ± 2 days

The following procedures will be performed:

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical examination and vital signs.
- ECOG performance status.
- Urine collection for pregnancy test on females of childbearing potential only. If positive then serum pregnancy test will be done.
- Blood sampling for the following:
  - Blood serum chemistry tests, CBC with Differential, ANC, platelet count
  - PK analysis sample collection pre-dose
  - Plasma and whole blood PD marker analysis sample collection pre-dose
- Overall response assessment.
- Administration of the morning dose of INCB018424.
- A study medication tablet count will be done to assess compliance. If patient qualifies for continued dosing, they will be provided with study medication for the next 4 weeks.
- Patients will be asked to return to the clinic on Day 1 of Cycle 3 (Day 28 of Cycle 2 ± 2 days). Patients will be asked to bring all study medication with them to the visit.
- Due to PK and PD samples being collected at the next visit, patients will be asked to withhold their morning dose of study medication on Day 1 of Cycle 3.
- All procedures listed above, including dispensing of study medication for next 4 weeks of Cycle 3, if patient qualifies for continued dosing, will be performed on Day 1 of Cycle 3 ± 2 days. Patients will be asked to return to the clinic on Day 1 of Cycle 4 (Day 28 of Cycle 3 ± 2 days). Patients will be asked to bring all study medication with them to the visit.
- Due to PD samples being collected at the next visit, patients will be asked to withhold their morning dose of study medication on Day 1 of Cycle 4.

- Review all safety information and criteria for dosing interruptions to determine if patients should receive further doses.
- Patients will be instructed to call the Investigator or designated research staff if they experience any "troubling" signs and/or symptoms that are of moderate or greater severity.

5.2.2.2 All Other Days

Patients will be instructed to have the following tests done at their local clinical laboratory at the frequency listed below:

- CBC with Differential, ANC, platelet count weekly i.e., Day 8, 15 and 22nd of Cycle 2 and 3.
- Blood Chemistry Chem-20 test Panel, every two weeks i.e., Day 15 of Cycles 2 and 3.
- The Investigator and/or research staff will immediately contact the patient to notify him/her to interrupt study medication if the laboratory test results meet the interruption criteria. The Investigator will continue to review the laboratory test results and inform the patients about how to proceed regarding study medication (i.e., re-starting or continue to hold).
- Patients will continue to self-administer study medication per instructions twice daily at approximately 12 hour intervals in an out-patient setting.

5.2.3 Each Subsequent Visit – Day 1

- All study visit specific observations as outlined in "Study calendar" and described for Day 1 of Cycle 2 and 3 will be done for each subsequent visit on Day 1.
- In addition, Day 1 of Cycle 4 the following procedures will be done:
  - Bone marrow aspiration or biopsy and cytogenetics (if abnormal prior to therapy) will be done (Cycle 4, Cycle 7 and each sixth subsequent cycle)
  - Plasma and whole blood PD biomarkers sample collection pre-dose
  - Cytogenetics may be performed on peripheral blood (if bone marrow aspiration is inadequate)
- A 3-month supply of study medication will be dispensed on Day 1 of each subsequent visit to qualified patients who have not met any interruption criteria and showing clinical benefit from the therapy.
- Patients will be instructed to return to the site every three months (+/- 7 days) following Day 1 of Cycle 4 and bring their study medication including empty containers with them.
- Patients will be instructed to go every two weeks for the next three months to their local laboratory to have blood drawn for CBC with Differential, ANC and platelet count.
- Due to PD samples being collected at the next visit, patients will be asked to withhold their morning dose of study medication on Day 1 of each subsequent visit.

- Patients will be instructed to call the Investigator or designated research staff if they experience any “troubling” signs and/or symptoms that are of moderate or greater severity.

5.2.4 Each Subsequent Visit – All Other Days

- Review all safety information and criteria for dosing interruptions on a regular and on-going basis to determine if patients should receive further doses.
- The Investigator and/or research staff will immediately contact the patient to notify him/her to interrupt study medication if the laboratory test results meet any interruption criteria. The Investigator will continue to review the laboratory test results and inform the patients about how to proceed regarding study medication (i.e., re-starting or continue to hold).
- The investigator and/or research staff will contact the patient on a regular monthly basis to assess the patient’s overall well-being, any new or worsening signs and/or symptoms, compliance with study medication and dosing instructions, compliance with the local laboratory schedule and to answer any questions that the patient might have. The investigator and/or research staff will remind the patient of their next scheduled visit and how to prepare for it (i.e., withhold their morning dose of study medication.) The investigator and research staff will be responsible for ensuring that all relevant information resulting from these monthly contacts is documented in the patient’s medical record and case report form, as appropriate.

5.2.5 End of Study or Early Termination Visit

- All study visit specific observations as outlined in “Study calendar” and described above for Day 1 of Cycles 2 and 3 will be done except:
  - Study medication will not be dispensed.
  - Blood draw for PK sampling will not be done.

5.2.6 Duration of Participation and Number of Subjects

The individual patient participation is expected to be 4-12 months. A maximum total number of 30 patients can be recruited into each disease category arm of this study and therefore the maximum total number of patients potentially studied under this protocol would be 120.

6. RESPONSE DEFINITIONS

Patients will be assessed for efficacy at the end of each 28 day cycle of therapy, +/- 4 days for the first 3 cycles, then 3 monthly thereafter.

6.1 Acute leukemias, MDS, CML-BP, CMML:

6.1.1 Complete remission: The patient must be free of all symptoms related to leukemia and have an absolute neutrophil count $\geq 1 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L, and normal marrow differential ($\leq$ 5% blasts) in a normo- or hypercellular marrow.

6.1.2 Partial remission: CR with 6-25% abnormal cells in the marrow or 50% decrease in bone marrow blasts.

6.1.3 CRp: As per CR but platelet count $<100 \times 10^9$/L.

6.1.4 Hematologic Improvement (HI)

Hematologic improvement should be described by the number of individual, positively affected cell lines
(e.g. HI-E; HI-E + HI-N; HI-E+ HI-P + HI-N).

6.1.4.1 Erythroid response (HI-E)

Major response: For patients with pretreatment hemoglobin less than 11 g/dL, greater than 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients, transfusion independence.

Minor response: For patients with pretreatment hemoglobin less than 11g/dL, 1 to 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients, 50% decrease in transfusion requirements.

6.1.4.2 Platelet response (HI-P)

Major response: For patients with a pretreatment platelet count less than 100×10^9/L, an absolute increase of 30×10^9/L or more; for platelet transfusion-dependent patients, stabilization of platelet transfusion independence.

Minor response: For patients with a pretreatment platelet count less than 100×10^9/L a 50% or more increase in platelet count with a net increase greater than 10×10^9/L but less than 30×10^9/L

6.1.4.3 Neutrophil response (HI-N)

Major response: For absolute neutrophil count (ANC) less than 1.5×10^9/L before therapy, at least a 100% increase, or an

absolute increase of more than 0.5 x 10^9/L, whichever is greater.

Minor response: For ANC less than 1.5 x 10^9/L before therapy, ANC increase of at least 100%, but absolute increase less than 0.5 x 10^9/L.

6.1.4.4 Progression/relapse after HI

One or more of the following: a 50% or greater decrement from maximum response levels in granulocytes or platelets, a reduction in hemoglobin concentration by at least 2 g/dL, or transfusion

6.2 CML response criteria

6.2.1 Hematologic Response (HR)

1. Complete Hematologic Response (CHR):
    a. WBC ≤ institutional upper limit of normal (ULN)
    b. Platelets ≤ 450,000 x10^9/L
    c. No blasts or promyelocytes in peripheral blood.
    d. < 5% myelocytes plus metamyelocytes in peripheral blood
    e. Peripheral blood basophils < 2%
    f. No extra-medullary involvement including no splenomegaly or hepatomegaly
    g. <5% blasts in bone marrow
2. No Evidence of Leukemia (NEL) - meet the same criteria as CHR except for:
    a. Platelets ≥ 20,000/mm3 and < 100,000 mm3, and/or
    b. ANC > 500/mm3 and < 1,000/mm3
3. Minor Hematologic Response (MiHR) - meet all of the following:
    c. < 15% blasts in BM and in PB
    d. < 30% blasts + promyelocytes in BM and PB
    e. < 20% basophils in PB
    f. No extra-medullary disease other than spleen and liver
4. Major Hematologic Response (MHR) is defined as CHR or NEL
5. Overall Hematologic Response (OHR) is defined as CHR, NEL or MiHR

A **confirmed** HR is obtained when all above criteria are fulfilled at least 28 days after they are first met.

6.2.2 Cytogenetic Response (CyR):
Classified according to suppression of the Philadelphia chromosome (Ph) by cytogenetics (FISH if cytogenetic analysis not informative, e.g., insufficient metaphases)
1. No cytogenetic response - Ph positive >95%
2. Minimal cytogenetic response - Ph positive 66-95%
3. Minor cytogenetic response - Ph positive 36-65%

4. Partial cytogenetic response - Ph positive 1-35%
5. Complete cytogenetic response - Ph positive 0%

* Major cytogenetic response = complete + partial (Ph positive ≤35%)

6.2.3 Molecular response

1. Major (MMR): BCR-ABL/ABL ratio ≤ 0.02%
2. Complete: Undetectable BCR-ABL

7. Pharmacokinetic and Pharmacodynamic Methods

7.1 Pharmacokinetic Methods

7.1.1 Blood Collection

On Days 1 of Cycle 1, PK blood samples will be obtained pre-dose, 0.5, 1, 1.5, 2, 4, 6 and if possible, 8 hours after administration of the morning dose of the study medication. PK samples will also be obtained pre-dose on Day 1 of Cycles 2 and 3. The exact date and time of the PK blood draws will be recorded along with the date and time of the last dose of study medication preceding the blood draw.

See Appendix F for specific information regarding the procedures for PK blood sample collection, processing and shipment.

7.1.2 Bioanalytical Methodology

The plasma samples will be analyzed for INCB018424 by a validated LC/MS/MS assay, carried out by Incyte Corporation (Wilmington, DE) or Incyte's designee.

7.1.3 Population Pharmacokinetic Analysis

The limited amount of plasma concentration data from this study, will be pooled with the results of a Phase 1 study in healthy volunteers to perform the population PK analysis. If there is sufficient demographic diversity in the population, an attempt will be made to evaluate the effect of demographic characteristics and baseline characteristics (e.g., age, weight, sex, race, renal function, smoking history, etc.) on the population PK profile.

7.2 Pharmacodynamic Method

7.2.1 Blood Collection

On Day 1 of Cycle 1 (at pre-dose and 2 hours after dose), and on Day 1 of Cycles 2 and 3 (pre-dose sample only) venous whole blood samples will be obtained for both whole blood and plasma PD markers according to the Study

calendar. Collection of a plasma PD sample will be done on Day 1 of subsequent cycles as described in Section 5.2. The exact date and time of the blood draws will be recorded along with the date and time of the last dose of study medication preceding the blood draw.

See Appendix F for specific information regarding the procedures for PD blood sample collection, processing and shipment.

7.2.2 Pharmacodynamic Analysis

The whole blood PD samples will be evaluated both unstimulated and following stimulation with a cytokine (e.g., IL-6) to activate the JAK/STAT pathways and then analyzed for both basal and activated levels of JAKs and STATs, including phosphorylated STAT3 and STAT5. Phosphorylated STAT3 and STAT5 will be measured using phospho-specific STAT3 and STAT5 ELISAs. For each patient, the percent inhibition of phosphorylated STAT3 and/or STAT5 will be calculated by comparing predose values with values obtained at different times after dosing. Additional PD markers (e.g., monitoring other cell signaling pathways, measuring specific cell populations or measuring cell surface markers that can be measured by flow cytometry, Western blot or ELISA) may be evaluated utilizing excess whole blood PD samples.

In addition, using the plasma PD sample, changes in plasma cytokine levels and markers of disease activity will be monitored over time using specific ELISAs. For each patient, the percent change in level will be calculated by comparing predose values with values obtained at different times after dosing. Additional PD markers (e.g., other cytokine levels, chemokine levels or other non-genomic protein markers that can be measured by Western blot or ELISA) may be evaluated utilizing excess PD or PK samples. These analyses will be carried out by Incyte Corporation (Wilmington, DE) or Incyte's designee.

7.3 Bone Marrow Aspiration, Biopsy and Cytogenetics

Bone marrow aspiration or biopsy will be taken pre-dose during the screening phase and at Day 1 ± 7 days of Cycle 4, Day 1 of Cycle 7 ± 7 days and thereafter on Day 1 ± 7 days of each 6th subsequent cycle. This includes staining and determination of cytogenetics if abnormal prior to therapy.

7.3.1 Bone Marrow Assessment

The bone marrow biopsy or aspirate should be assessed by an experienced hematopathologist using his/her standard examination. Bone marrow evaluation will include staining, cytogenetics if abnormal prior to therapy and mutation analysis if present prior to therapy.

7.3.2 Cytogenetics

Cytogenetic studies will be repeated only in patients with abnormalities at baseline on Day 1 of Cycle 4, Day 1 of Cycle 7 and thereafter on Day 1 of each 6th subsequent cycle. This will be generally done on the bone marrow samples provided at the defined time points but may also be done on peripheral blood collected at these time points in the event bone marrow aspirate could not be obtained. The cytogenetic testing laboratory will provide specific instructions to the Investigators.

8. REGULATORY AND REPORTING REQUIREMENTS

Adverse event reporting will be as per the current NCI criteria and the MDACC Adverse Event Reporting Policy for Leukemia Phase I and early Phase II studies.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html).*

Serious Adverse Event Reporting (SAE)

A serious adverse event is – any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or Sponsor.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must by reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy ". SAEs must be reported to the IRB and the Sponsor (Safety Project Manager) regardless of attribution.

- **All life-threatening or fatal events** with possible, probable or definite attribution to the study drug must have a written report faxed within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the Office of Research Education and Regulatory Management (ORE&RM) (fax 713-792-9631). The sponsor representative should be notified by phone at 713-563-0379 to confirm receipt of the fax.

- **The MDACC Internal Adverse Event Reporting Form will be used for reporting to the IRB and the Sponsor (Safety Project Manager ORE&RM).**

- **Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory test have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IRB and the Sponsor (Safety Project Manager ORE&RM). This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the Sponsor (Safety Project Manager ORE&RM) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

8.1 Expedited Adverse Event Reporting

Leukemia associated symptoms are not to be reported as adverse events on this protocol. Myelosuppression and associated complication are expected events during leukemia therapy and are part of the treatment success (marrow emptying of leukemia cells). Therefore, myelosuppression and associated complications such as fever, infections, bleeding, and related hospitalization will be reported in the study summary. Only prolonged myelosuppression, as defined by the NCI criteria specific for leukemia, i.e. marrow cellularity <5% on day 42 or later (6 weeks) from start of therapy without evidence of leukemia, will be reported as an SAE and considered in defining the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT). Admission to the hospital for administration of a new cycle of treatment does not require expedited reporting. SAEs occurring in patients registered to the trial but not receiving any protocol agents (ie occurring before protocol treatment) do not require expedited reporting.

For this protocol, the following adverse events are specifically excluded from expedited AE reporting:

CTCAE Category	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Comments
Blood/Bone marrow/ Infection	↓Hemoglobin, leukocytes (total WBC), lymphopenia, ↓neutrophils/ granulocytes (ANC/AGC), ↓ platelets, fever, sepsis	1-4	Yes	Do not require expedited reporting
Gastrointestinal	Diarrhea, nausea, vomiting, stomatitis	1-3	Yes	Hospitalization for grade 3 AEs does not require expedited reporting
Metabolic/laboratory	↓K,↓Mg, ↓Na, ↓glucose, ↑K, ↑Mg, ↑glucose, ↑uric acid,↑LDH Or other metoablic indeces	1-4	Yes	Do not require expedited reporting unless hospitalized for management

9. STATISTICS

9.1 Study Population

All patients who received at least one dose of study medication will be included in the safety analyses.

9.1.1 Selection of Sample Size

This phase II study will use a Gehen's design. Assuming a null response rate of 0%, targeting a 15% response rate and power=80%, the trial will initially enroll 10 patients in each disease category: 1) AML; 2) ALL; 3) MDS; and 4) CML. If at least one response is achieved in the 10 patients in a disease

Category, then a total of 30 patients will be enrolled in this disease category. Thirty patients will provide a confidence interval for response rate with half-width=0.13, assuming the true response rate is 15%. The total sample size is 120.

For toxicity evaluation, patients enrolled in the study will be considered in 2 cohorts (I) those with relapsed/refractory AML, ALL, and MDS (including CMML), and blast phase CML, and (II) those with chronic phase CML. At any time after 6 patients are enrolled in cohort I (including AML, ALL, MDS, blast phase CML patients), if 30% or more patients experience grade 3 or 4 toxicity thought to be directly related to INCB018424 and lasting longer than 2 weeks, then we will stop that cohort of the trial. At any time after 6 patients are enrolled in cohort II (including chronic phase CML patients), if 15% or more patients experience grade 3 or 4 toxicity thought to be directly related to INCB018424 and lasting longer than 2 weeks, then we will stop that cohort of the trial.

9.2 Efficacy and PK/PD Variables

The efficacy variables include

- Clinical response
- Cytogenetic response
- The PK and PD variables will include:
  - Determination of the PK of INCB018424 by measuring plasma concentration time profiles.
  - Determination of PD markers including % inhibition of STAT3/5 protein phosphorylation

9.2.1 Efficacy and PK/PD Analysis

Efficacy analyses will be exploratory in nature. All efficacy measures will be estimated with 95% confidence intervals at the dose used in the expanded cohort. The clinical response and the hematological response will be estimated with 95% confidence intervals at each time point. The response rates over time may be analyzed graphically or using a statistical model.

The PK parameters of INB018424 will be summarized using descriptive statistics, and the log-transformed INCB018424 PK parameters will be compared using a 1-factor analysis of variance. The mean values of the PK parameters may be compared to historical data in healthy volunteers to determine if the INCB018424 PK profile is different between patients with hematological malignancies and healthy patients.

For each patient who has taken study medication, the PD parameters will be calculated to explore preliminary evidence of PD activity by assessing the

effect of INCB018424 on pre- and post-dose. If the p-STAT3/5 signaling data are sufficiently robust, an exploratory PK/PD analysis will be performed.

9.3 Safety Analysis

The clinical safety data (vital signs, ECGs, routine laboratory tests and adverse events) will be analyzed using summary statistics (e.g., mean, frequency) and no formal statistical comparisons among the treatment groups are planned.

9.3.1 Adverse Events

Severity of adverse events will be based on the NCI–CTCAE v3.0 (NCI Common Terminology Criteria for Adverse Events, Publ. Aug 9, 2006). The subset of adverse events that are considered by the Investigator to have a possible or probable relationship to study medication will be considered to be treatment-related adverse events. If the Investigator does not specify the relationship of the adverse event to study medication, the adverse event will be considered to be treatment-related. The incidence of adverse events and treatment-related adverse events will be tabulated.

9.3.2 Clinical Laboratory Tests

Laboratory test values outside the normal range will be assessed for drug association based on screening and baseline values and 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.

9.3.3 Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, heart rate, respiratory rate and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities and patients exhibiting clinically notable vital sign abnormalities that were not present at screening or baseline will be listed.

9.4 Study Definitions

Survival, time to progression, time to treatment failure, and duration of response will be presented using Kaplan-Meier curves for each patient group

9.4.1 Survival

"Survival" is defined as the period of time from date of first study drug administration to the date of death or date patient withdrawn from study.

9.4.2 Time to Progression

"Time to Progression" is defined as the period of time from the date of first study drug administration to the date that the patient is withdrawn because of clinical or radiographic progressive disease or death from any cause.

9.4.3 Time to Treatment Failure

"Time to Treatment Failure " is defined as the period of time from the date of first study drug administration to the date of withdrawal from the study for any reason other than study closure.

9.4.4 Duration of Response

"Duration of Response " is defined as the period of time from the date of first objective response to the date of progression. "Duration of Response" is defined for patients with an objective response only.

9.4.5 Time to Response

"Time of Response " is defined as the period of time from the date of first study drug administration until the first objective documentation of response.

9.4.6 Intent-to-Treat Data Set

The Intent-to-Treat Data Set will include all patients who receive at least one dose (full or partial dose) of study drug.

9.5 Reporting and Exclusions

9.5.1 Evaluation of toxicity**.**

All patients will be evaluable for toxicity from the time of their first treatment with INCB018424.

9.5.2 Evaluation of response**.**

All patients included in the study must be assessed for response to treatment, unless there are major protocol treatment deviations or they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other

cause, or 8) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

10.0 ETHICS

10.1 Institutional Review Board or Ethics Review Committee

It is the responsibility of the Investigator to assure that all aspects of the ethics review are conducted in accordance with the current Declaration of Helsinki as described in the International Conference on Harmonisation (ICH) E6: Guideline for Good Clinical Practice (GCP), and/or local laws, whichever provides the greatest level of protection for the study participants. The protocol and any information supplied to the patient to obtain informed consent, including written informed consent form(s), patient recruitment procedures (e.g., advertisements), and written information to be provided to patients (information leaflets), must be reviewed and approved by a qualified IRB/ERC prior to enrollment of participants in the study.

Amendments to the protocol and revisions to the informed consent must also be submitted to and, if required, approved by the IRB/ERC.

At intervals required by the IRB/ERC, but not less than annually, the Investigator must submit to the IRB/ERC a progress report with a request for re-evaluation and re-approval of the study.

After completion or termination of the study, the Investigator must submit a final report to the IRB/ERC. This report should include: deviations from the protocol, the number and types of participants evaluated, the number of participants who discontinued (with reasons), results of the study, if known, and significant adverse events, including deaths that occurred during the conduct of the study.

The Investigator, as part of the records retention requirements for the study, must maintain documentation of all submissions, correspondence, and approvals to and from the IRB/ERC.

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

10.2 Informed Consent

Before being enrolled in the clinical study, patients must consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them.

An informed consent document that includes both information about the study and the consent form will be prepared and given to the patient. This document will include all elements required by the ICH, GCP, and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the Investigator must have the IRB/ERC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the patients.

The document must be in a language understandable to the patient and must specify who informed the patient. Where required by local law, the person who informs the patient must be a physician.

After reading the informed consent document, the patient must give consent in writing. The patient's consent must be confirmed at the time of consent by the personally dated signature of the patient and by the personally dated signature of the person conducting the informed consent discussions.

If the patient is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to patients must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the patient or by a local legally recognized alternative (e.g., the patient's thumbprint or mark). The witness and the person conducting the informed consent discussions must also sign and personally date the consent document.

A copy of the signed consent document must be given to the patient. The original signed consent document will be retained by the Investigator.

The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

The Investigator must inform the patient's primary physician about the patient's participation in the trial if the patient has a primary physician and if the patient agrees to the primary physician being informed.

10.2.1 Update of Informed Consent

The informed consent and any other information provided to patients or the patient's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the patient's consent, and should receive IRB/ERC approval/favorable opinion prior to use. The Investigator, or a person designated by the Investigator should fully inform the patient or the patient's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue

participation in the study. This communication should be documented. During a patient's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the patient.

REFERENCES

1. Ravandi F, Kantarjian H, Giles F, Cortes J. New agents in acute myeloid leukemia and other myeloid disorders. Cancer. 2004;100:441-454.
2. Faderl S, Jeha S, Kantarjian HM. The biology and therapy of adult acute lymphoblastic leukemia. Cancer. 2003;98:1337-1354.
3. Garcia-Manero G, Faderl S, O'Brien S, Cortes J, Talpaz M, Kantarjian HM. Chronic myelogenous leukemia: a review and update of therapeutic strategies. Cancer. 2003;98:437-457.
4. Ravandi F, Talpaz M, Estrov Z. Modulation of cellular signaling pathways: prospects for targeted therapy in hematological malignancies. Clin Cancer Res. 2003;9:535-550.