Oregon Health & Science University
OHSU Knight Cancer Institute
IRB Protocol #:7195
BMS Protocol #: CA180-392
Ariad Protocol #: AP24534-13-014
ClinicalTrials.gov #: NCT01620216

TITLE:
A Phase II Proof-of-Concept Trial to Study Kinase Inhibition in Relapsed/Refractory Acute Leukemias: Using a Comprehensive In Vitro Kinase Inhibitor Panel to Select Individualized, Targeted Therapies

Coordinating Center: Oregon Health & Science University (OHSU)

Principal Investigator: Marc Loriaux, MD, PhD
Associate Professor
Division of Hematology and Medical Oncology
BRB507
Oregon Health and Science University
3181 SW Sam Jackson Pk Rd
Portland Oregon, 97239
Email: loriauxm@ohsu.edu
(503) 494-9383

Clinical Principal Investigator: Stephen E.F. Spurgeon, MD
Associate Professor of Medicine
Division of Hematology and Medical Oncology
Knight Cancer Institute
(503) 494-8950

Subsites:

Institution	Responsible Investigator	Phone	Email
University of Utah Huntsman Cancer Center	Tibor Kovacsovics, MD	801-585-3229	tibor.kovacsovics@hci.utah.edu
National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI)	Christopher S. Hourigan, MD, DPhil, FACP	301-803-8029	hourigan@nih.gov
University of Texas-Southwestern	Robert Collins, MD	214-648-4155	robert.collins@utsouthwestern.edu

Statistician: Motomi Mori, PhD
Biostatistics Shared Resource
Knight Cancer Institute
(503) 418-1555

Study Coordinator/ Central Contact: Tara Macey, PhD
Center for Hematologic Malignancies
Oregon Health & Science University

	Phone: 503-494-4603 or 503-494-9916 Fax: 503-346-8025
Supplied Agent:	Dasatinib, Sorafenib, Sunitinib, Ponatinib, Pacritinib, Ruxolitinib, and Idelalisib
IND/IDE:	IDE: G110198
Original Protocol Date:	3/19/2012
Protocol Revision Dates:	7/10/2015, 06/29/2016, 11/22/2016

SCHEMA

Eligibility
Relapsed or treatment refractory acute leukemia

Treatment Sensitivity Screening
Evaluate primary acute leukemia sample for sensitivity to a panel of tyrosine kinase inhibitors.
Screening may take 4-10 days
(See Section 10.1)

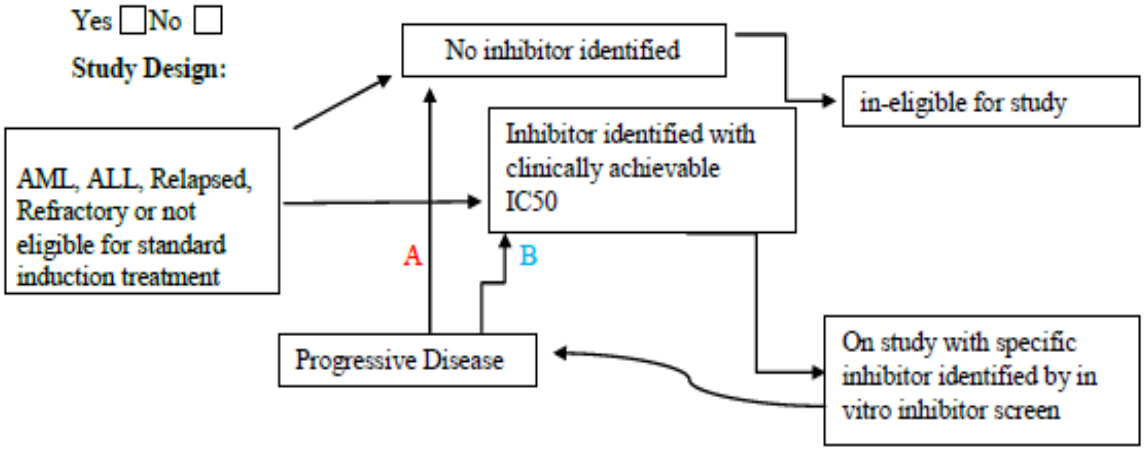
Patients eligible for treatment with study drug
The treatment cycle is 28 days.
Subject may remain on drug as long as there is therapeutic benefit.

End of treatment or early discontinuation or Re-screen
The treatment cycle is 28 days.
Subject will be removed from study when there is no longer therapeutic benefit

The subject may rescreen for drug sensitivity and trial re-entry
The treatment cycle is 28 days.
Subject may remain on drug as long as there is therapeutic benefit.

End of study

OVERVIEW OF STUDY DESIGN



A: After progressing on inhibitor, and if no additional inhibitor identified, will be removed from study.

B: After progressing on inhibitor, if additional inhibitor identified, will be eligible to proceed on treatment with additional inhibitor.

Leukemic samples (peripheral blood or bone marrow) from patients with known or suspected relapsed acute leukemia (ALL or AML) will be processed to enrich for mononuclear cells. Using our kinase inhibitor plates, the IC_{50} for each kinase inhibitor will be calculated and the results analyzed to determine if one of the study drugs could be an effective treatment for an individual leukemia patient. If the screen identifies a single inhibitor that has a clinically achievable IC50, e.g. inhibitor "A," and the patient meets the eligibility criteria, then they will be treated with inhibitor "A." If the inhibitor screen identifies multiple treatment options and the patient meets the eligibility criteria for all possible therapeutics screened, then the "most effective drug" will be assessed using additional sensitivity parameters including: comparison with the range of results from other responders for each candidate drug, evaluation of best level of inhibition (IC_{75}, IC_{90}), and evaluation of additional curve fitting parameters (i.e., slope and area under the curve). Patients may only receive one inhibitor at a time while on study. However, if a patient's diseaseprogresses (defined as a $\geq$ 50% increase in leukemic bone marrow blasts) while on one inhibitor, then he/she is eligible to re-enroll on study if, at the time of progression, a) another potential inhibitor (inhibitor "B") is identified on repeat inhibitor plate testing using mononuclear cells obtained at time disease progression and b) the patient still satisfies all the study eligibility criteria.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objective

To determine the clinical activity of kinase inhibitors using pre-clinical (in-vitro) activity to select individual therapy. Clinical activity will be defined as $\geq$ 25% decrease in bone marrow or peripheral blood blast counts.

1.2 Secondary Objectives

1. To evaluate overall objective response rates (complete response plus partial response).
2. Determine overall survival (OS) and progression-free survival (PFS).

1.3 Exploratory/Correlative studies

1. Prioritize active/aberrant kinase pathways using an in vitro inhibitor screen using individual primary leukemia samples.
2. Measure 'on target' in vivo kinase inhibition and STAT-5 phosphorylation and correlate with response to treatment.
3. Perform Next Generation sequencing (whole exome sequencing) for complete mutational analysis
4. Identify aberrant gene expression in primary leukemia samples from study subjects.
5. Evaluate pharmacokinetics for each individual kinase inhibitor during therapy.

2.0 BACKGROUND

2.1 Acute Leukemias

2.1.1 Relapsed/Refractory AML

Currently, there is no standard treatment for relapsed/refractory leukemia and studies including relapsed/refractory disease are heterogeneous. Short, relapse-free intervals, poor cytogenetics, advanced age at relapse, and the absence of transplant in first remission all contribute to the poor long term outcomes in these patients after initial induction and consolidation therapy (1). Further, if patients are refractory to initial therapy and/or require a second salvage therapy, outcomes are extremely poor. For example, a retrospective analysis study of 594 patients with AML undergoing second salvage therapy with standard therapies including stem cell transplant reported a median survival of 1.5 months with a one-year survival of 8%. Among those attaining a complete remission (CR), which was 13% of the population, the CR duration was only 7 months. On multivariate analysis, a number of poor prognostic features were identified including: age > 60, initial CR duration < 12 months, and second CR duration < 6 months (2). Importantly, standard therapies do not appear to favorably impact patients who relapse in < 12 months (3, 4)}. Therefore, this is a population in need of novel treatment approaches.

Based on existing data and national guidelines, the general recommended treatment paradigm for patients with relapsed/refractory leukemia is enrollment into clinical trials or best supportive care if patients have refractory disease or a remission lasting < 12 months (since the initiation of therapy). Conversely, patients with remissions > 12 months have significant responses with re-induction and/or salvage chemotherapy regimens. So, although clinical trials are encouraged, standard treatment options may lead to favorable outcomes (5) (6). We have used this paradigm

as a guideline for the inclusion criteria for this trial.

2.1.1.1 AML in the elderly and/or unfit

Elderly patients with acute leukemia have poor outcomes and thus remain a significant therapeutic challenge. Although 30-40% of elderly patients with AML will achieve a CR with standard induction, the median survival in this population is around 10 months (7). The worst outcomes in this population have been attributed to high risk cytogenetics, higher rates of secondary leukemia, increased multi-drug resistance, decreased performance status, significant co-morbidities, as well as poorly defined benefits of post remission consolidation, and a high treatment related mortality (7-10). To better understand why elderly patients have worse outcomes, a number of prognostic factors have been evaluated and prognostic scores have been developed that incorporate both disease related and patient related factors. Based on these results, older AML patients can be categorized as "fit" or "unfit" for standard induction chemotherapy. For example, a patient >70 years old with poor performance status (ECOG >3) may have a treatment related mortality of 60-70% with standard induction. As a result, elderly patients are often not candidates for standard cytotoxic therapies; especially in the relapsed or refractory setting, and are less likely to receive chemotherapy and/or to be entered on clinical trials (11). In the face of these challenges it is imperative that elderly patients be treated on novel clinical trials. In fact, currently the NCCN treatment guidelines recommend that whenever possible, all AML patients should be offered clinical trial participation, especially in patients > age 60 with poor risk disease features or a poor performance status (i.e. ECOG > 2) (12).

Progress has been seen with the use of hypomethylating agents (azacytidine, decitabine) for the treatment of elderly AML patients who are unfit for chemotherapy. For example, Decitabine, a hypomethylating agent, when used as front-line therapy in elderly patients with AML in a phase II trial had an ORR of 26% and CR of 24%, along with an acceptable toxicity profile (13). In addition, a randomized international phase III trial (Study AZA PH GL 2003 CL 001) for higher-risk MDS patients, comparing azacytidine to a conventional care regimen (CCR) in high-risk MDS, included 34% patients with RAEB-T/AML WHO, which would be considered to have a diagnosis of AML by current diagnostic criteria. This study demonstrated superior overall survival compared to CCR, with a median overall survival of 24.4 months for azacytidine vs. 15 months for CCR, a benefit that persisted for RAEB-T/WHO AML cases. Based on these results, hypomethylating agents are an appropriate and frequently utilized off study therapy in unfit elderly patients with AML.

2.1.2 Relapsed/Refractory Acute Lymphoblastic Leukemia (ALL)

Outcomes in adults with relapsed ALL are extremely poor. Two large series demonstrate the challenge of recurrent ALL and highlight the point that the overwhelming majority of patients cannot be successfully salvaged with current therapies. Of 1372 adults with ALL initially treated on the MRC UKALL/ECOG 2933 protocol who achieved a complete remission, 609 (44%) relapsed. In this series the median survival after relapse was only 24 weeks and only 7% were long term survivors (14). In another study of 922 adult ALL patients treated per the LALA-94 trial as initial therapy, 421 (54%) developed relapsed disease. Although 44% of patients who relapsed achieved a second complete remission, the median disease free survival was only 5.2 months and the median survival was 6.3 months. Only 12% of patients in this series had favorable long term outcomes, the majority of which were achieved after allogeneic stem cell

transplantation (15). Given these results, it is largely accepted that relapsed ALL is incurable with current standard chemotherapy regimens. As many of these patients will not respond to salvage chemotherapy and/or are not candidates for transplantation, this is another population also in need of novel therapeutic approaches.

2.2 Study Agents - Product Background and Mechanism of Action

2.2.1 Dasatinib

Dasatinib (Sprycel®) is an abl/src kinase inhibitor FDA approved for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase Philadelphia chromosome-positive (Ph^+) chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib, and adults with Ph^+ ALL with resistance or intolerance to prior therapy.

2.2.2 Sunitinib

Sunitinib (Sutent®) is a tyrosine kinase inhibitor that is FDA approved drug for the treatment of renal cell carcinoma, gastrointestinal stromal cell tumor, and pancreatic neuroendocrine tumor in patients with unresectable locally advanced or metastatic disease.

2.2.3 Sorafenib

Sorafenib (Nexavar®) is a tyrosine kinase inhibitor that is FDA approved and marketed for the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment. It has also been used in combination with chemotherapy and hypomethylating agents in AML but is not FDA approved for this indication.

2.2.4 Ponatinib

Ponatinib (Iclusig®) is an abl/src kinase inhibitor indicated for the treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph^+ ALL and treatment of adult patients with chronic phase, accelerated phase, or blast phase CML or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.

2.2.5 Pacritinib

Pacritinib is an oral TKI with activity against two important activating kinases in the Janus Associated Kinase family (Janus Associated Kinase 2 [JAK2] and FMS-like tyrosine kinase 3 [FLT3]) that are activated in some patients with AML. The JAK family of enzymes is a central component in signal transduction pathways, which are critical to normal blood cell growth and development as well as inflammatory cytokine expression and immune responses. Activating JAK2 mutations are implicated in certain blood-related cancers, including myeloproliferative neoplasms (MPNs), leukemia, and certain solid tumors. FLT3 is a gene commonly found mutated in patients with acute myeloid leukemia (AML). In AML, FLT3 mutations are the most frequent genetic mutations observed, and are involved in the signaling pathway of autonomous proliferation and differentiation block in leukemia cells. As both a JAK2 and FLT3 inhibitor, pacritinib provides a dual inhibitory role that may prove to be a promising therapeutic strategy.

Pacritinib is unique among JAK inhibitors in that it also inhibits IL-1 Receptor Kinase-1 (IRAK-1), a protein previously shown to be critical in myelodysplasia, and is also active in AML blasts where IL-1 is a stimulatory and survival cytokine. Pacirtinib also inhibits colony stimulating factor-1 receptor (CSF-1R) kinase, which may be an important stimulant in AML cells with monocytoid features.

2.2.6 Ruxolitinib

Ruxolitinib (INCB018424 phosphate, INC424, ruxolitinib phosphate) represents a novel and potent inhibitor of JAK1 and JAK2. The inhibitory characteristics of ruxolitinib is characterized by a 50% inhibitory concentration (IC_{50}) of 3.3 ± 1.2 nM for JAK1, and an IC_{50} of 2.8 ± 1.2 nM for JAK2. This is in comparison with modest to marked selectivity against TYK2 (tyrosine kinase 2) (IC_{50}=19 ± 3.2 nM) and JAK3 (IC_{50}=428 ± 243 nM), respectively. Ruxolitinib has been granted Marketing Authorization Approval in the USA (approved in November 2011) for the treatment of intermediate or high-risk myelofibrosis, including PMF, post–polycythemia vera myelofibrosis and post–essential thrombocythemia myelofibrosis. Ruxolitinib was subsequently approved in December 2014 for the treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

2.2.7 Idelalisib

PI3Kδ is a central signaling enzyme that mediates the effects of multiple receptors and is critical for primary survival, proliferation, and homing signaling pathways active in malignant B-cells. Idelalisib (Zydelig®) is a PI3Kδ inhibitor that received accelerated approval by the US FDA for the treatment of patients with relapsed follicular lymphoma (FL) and Small Lymphocytic Lymphoma (SLL) who have received at least 2 prior systemic therapies. Idelalisib is fully approved to be used in combination with rituximab for the treatment of patients with relapsed CLL, in whom rituximab alone would be considered appropriate therapy due to other co-morbidities. Responses for SLL and FL were reported at 58% (0% CR) and 54% (8% CR) respectively with a duration of response of 11.9 months in SLL and not evaluable in FL. In CLL, the hazard ratio for PFS was 0.18 (95% CI; 0.10, 0.32) compared to rituximab alone (16). Idelalisib as monotherapy or in combination with other agents (such as bendamustine, chlorambucil) and immunotherapy (rituximab, ofatumumab) is shown to be tolerable and demonstrated clinical efficacy in clinical trials in patients with indolent (i) non-hodgkins lymphoma (iNHL) and CLL(17, 18). Idelalisib has not yet been widely studied in AML; however, PI3K/AKT signaling is important to AML and ALL leukemogenesis (19, 20) and we have observed pre-clinical anti-AML activity using our in vitro assay.

2.3 Study Rationale

Aberrant kinase signaling promotes leukemogenesis suggesting that kinases are potential therapeutic targets. However, identifying one specific molecular target in acute leukemias has remained elusive, suggesting that multiple kinase pathways are important and that the mechanism of aberrant kinase activation may be unique in many patients. Further, it is likely that over time, standard therapy may select for specific malignant clones that depend on altered kinase signaling pathways throughout the course of the disease. Thus, it is imperative that we elucidate which kinase signaling pathways are important in individual patients and tailor their therapy accordingly.

Recent developments highlight the importance of aberrant kinase-mediated signaling pathways in acute leukemia. The incorporation of the bcr-abl kinase inhibitors imatinib and dasatinib to standard chemotherapy in Ph^+ALL and FLT-3 kinase inhibition in acute AML have found to be effective in certain leukemia patients. In addition to showing therapeutic promise, inhibition of these targets provides the "proof of principle" that molecular pre-identification of activating kinase pathways can be translated to improved therapeutic outcomes.

Understanding the mechanisms underlying leukemia pathogenesis is an ongoing challenge but is the first step in developing more effective therapies for individual leukemia patients. Despite realizing that leukemia is unique in each patient, interventional trials continue to be applied to populations instead of individuals. Thus, it is clear that personalized treatment approaches and new study designs, which utilize evolving "real-time" information/feedback to rapidly inform individualized treatment decisions, are needed. With this in mind, we have developed a small molecule kinase inhibitor screen to rapidly identify therapeutic tyrosine kinase targets in leukemia patients while simultaneously providing individualized therapeutic options.

The next step is to translate pre-clinical findings to patient care. The ability to rapidly identify patient-specific, commercially available (i.e., FDA approved) oral agents is easily amenable to clinical application. Relapsed/refractory leukemia is an excellent model to use because: 1) outcomes with standard therapies are poor, 2) sample acquisition (e.g. from blood or bone marrow) and processing are simple and standardized which allows for easy and rapid pre-clinical (ex-vivo) identification of important kinase targets, 3) clinical activity can be easily monitored via changes in bone marrow or peripheral blast counts, and 4) in-vivo kinase target validation can be measured frequently and in real time. By using our pre-clinical assay to identify individualized leukemia therapies, we will provide an important contribution to the goal of applying patient-tailored kinase inhibitors to all leukemia patients.

If the ex-vivo screen can predict clinical activity, we hope to use this protocol as a template for the rapid identification of novel kinase inhibitors for individualized leukemia therapy (alone, in combination, or with chemotherapy).

2.4.1 The Ex-Vivo Small Molecule Kinase Inhibitor Screen

The kinase inhibitor screen is a function-first, ex vivo assay that can identify potentially useful individualized treatments for patients with leukemia. Our screen currently utilizes approximately 130 small-molecule, cell-permeable compounds including a core of 38 tyrosine kinase inhibitors that collectively target the majority of the tyrosine kinome. These core inhibitors have been screened against 300 of the 500 kinases in the kinome to determine their target specificities (21). Many of the compounds in the inhibitor screen are commercially available or are in clinical development.

For these screens, enriched mononuclear cells from patients with known or suspected acute leukemia are plated in 384-well plates containing small-molecule inhibitors at serial dilutions spanning a concentration range that includes the predicted IC_{50}. Cell viability is measured after a three-day incubation. The viability data is normalized to untreated controls and the IC_{50} for a given inhibitor is compared with the median IC_{50} values from all leukemia samples assayed. The results are available within 3-4 days allowing for the patient-specific identification of kinase inhibitors in a clinically relevant time frame.

By applying the pre-clinical assay to individualized leukemia therapy, we hope to provide an important contribution to the goal of applying patient-tailored kinase inhibitors to all leukemia patients. Crucial to developing this platform is taking the initial step of prospectively using this assay to pre-select which inhibitors may be effective for individual patients. Therefore, we will be conducting a clinical trial in patients with relapsed/refractory leukemia who first demonstrate in vitro kinase inhibitor sensitivity identified using the inhibitor screen as outlined above.

2.4.2 Kinase Inhibitors in Acute Leukemia

In Ph^+ ALL, by targeting Bcr-Abl, the addition of kinase inhibitors to chemotherapy has improved outcomes. The role of kinase inhibition in other leukemias is less clear; however, an evolving understanding of the underlying leukemogenesis has led to an increasing number of targeted therapeutic approaches. For example, FMS-like tyrosine kinase 3 (FLT3), a receptor tyrosine kinase expressed in AML has been shown to be activated by internal tandem duplications (ITD) in some patients(14). This has led to the development of FLT-3 directed kinase inhibitors which show significant in vitro activity against FLT3-ITD, and have initially shown some success in clinical trials. For example, Single agent administration of the first generation inhibitors PKC412, in relapsed AML patient with mutated FLT3-ITD, was associated with clinical activity (15). A second generation FLT3 inhibitor, AC220, with higher affinity and an improved pharmacokinetic profile, has been associated to a 50% response rate, including some CRs, in patients with relapsed AML with FLT3-ITD, demonstrating the potential of targeted therapy in AML (22, 23).

Kinase inhibitors as single agents in treating acute leukemias have shown activity and. Both dasatinib and sunitinib have been used as single agents in unselected patients with AML. Dasatinib yielded a complete response in 1 of 9 (11%) patients, while 6 of 15 (40%) patients responded to sunitinib, but in both cases responses were brief (24, 25). Likewise, sorafenib has shown anti-leukemic activity, with a best response of stable disease observed in 11 of 15 patients. Although no complete or partial responses were observed with sorafenib, bone marrow counts decreased in 40% of treated patients (26). Pacritinib has not yet been studied in AML; however, it has shown significant activity in patients with myelofibrosis (27).

In vitro results using our kinase assay platform shows that approximately 70% of samples demonstrate strong sensitivity to one or more inhibitors, and approximately 40% of samples have sensitivity to at least one commercially available drug. Importantly, the results yielded from this platformshow a heterogeneous inhibitor sensitivity profiles even within diagnosis groups; thus further supporting a need for individualized targeted therapies. In adult acute leukemias, the most common drug identified in these screens was dasatinib, with 24% of samples showing sensitivity. Twenty-three percent of samples were sensitive to sunitinib, and approximately 22% showed a high level of sensitivity to ponatinib. Another 12% of samples showed inhibitor sensitivity to sorafenib. Notbaly, the addition of ponatinib provides treatment coverage for up to 44% of relapsed/refractory acute leukemia patients, and in a treatment cohort of 24 patients, up to five may be eligible for ponatinib treatment. A nearly identical coverage was also seen in a smaller cohort of relapsed acute leukemia patients. To date, we have also observed a response rate of ~85% among 46 AML samples treated with pacritinib.

Over the course of 2007-2016, we have tested ruxolitinib for sensitivity on 491 patient samples

with an AML diagnosis and on 157 patient samples with an ALL diagnosis. Approximately 7% (32/491) of the AML samples were sensitive to Ruxolitinib, and another ~2.5% (4/157) of the ALL samples were similarly sensitive.

Idelalisib sensitivity was tested on 567 patient samples with an AML diagnosis and on 228 patient samples with an ALL diagnosis (2007-2016). Approximately 13% (73 of 567) of the AML samples were highly sensitive to idelalisib with IC_{50} values less than 0.1 μM. Approximately 15%,or 33 of 228, of tested ALL samples were sensitive to idelalisib with IC_{50} values less than 0.1 μM.

We are currently working with industry partners to add other commercially available drugs and multi-kinase inhibitors in early clinical development. The addition of these drugs could collectively increase coverage to over 50% of samples.

2.4.3 Using the inhibitor kinase sensitivity assay to select treatment

There are no prospective and/or published data on using the small molecule inhibitor screen to select which patients may benefit from specific therapies. However, one case study supports this treatment approach. On a compassionate use basis (case report in preparation), a child with multiply relapsed juvenile myelomonocytic leukemia after multiple courses of chemotherapy and 2 rounds of allogenic transplant, was treated according to the results of OHSU's in vitro assay. At that time, a biologic sample obtained from this patient for *ex vivo* drug sensitivity was profiled using the inhibitor panel. The inhibitor assay revealed extreme sensitivity to dasatinib with an IC_{50} 100-times lower than the median dasatinib IC_{50} for 120 other primary leukemia samples (Figure 1A). Subsequent treatment with dasatinib resulted in the patient having a rapid decrease in WBC count to within normal range (figure 1B). One month after starting dasatinib the patient presented with fevers and leukocytosis. A repeat marrow at the time showed no overt evidence of disease (Figure 1C), whereas cytogenetic studies identified a persistent clonal population. A blood culture at that time grew *Klebsiella*. Once treatment for bacteremia was initiated the patient had a slow resolution of his leukocytosis. Despite his aggressive disease, the patient had been continuously treated with dasatinib for over four months without disease progression which allowed for him to receive a 3rd stem cell transplant.

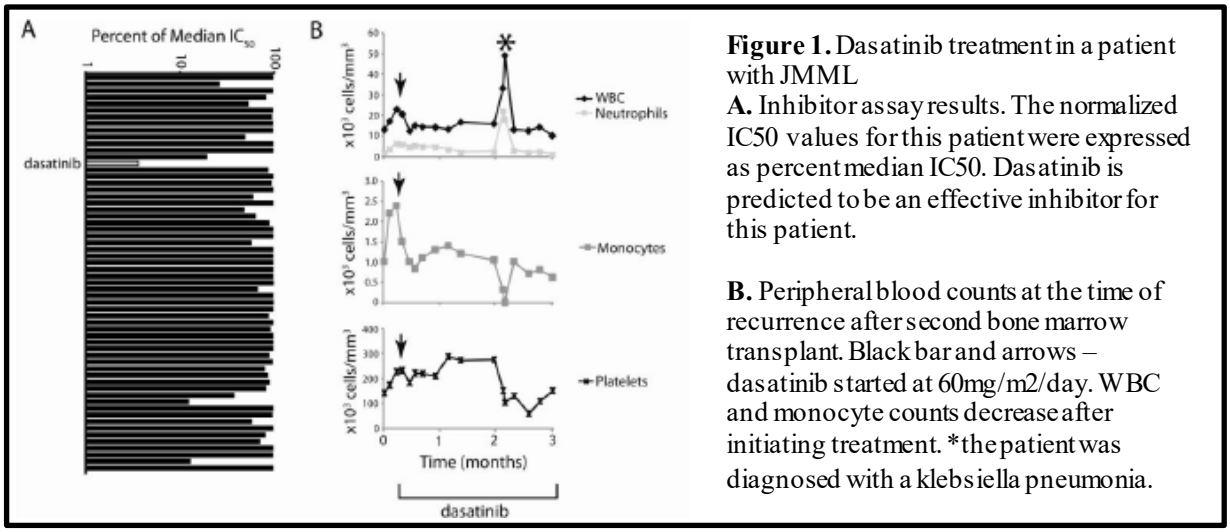


Figure 1. Dasatinib treatment in a patient with JMML
A. Inhibitor assay results. The normalized IC50 values for this patient were expressed as percent median IC50. Dasatinib is predicted to be an effective inhibitor for this patient.

B. Peripheral blood counts at the time of recurrence after second bone marrow transplant. Black bar and arrows – dasatinib started at 60mg/m2/day. WBC and monocyte counts decrease after initiating treatment. *the patient was diagnosed with a klebsiella pneumonia.

2.4 Correlative Studies Background

2.4.1 Druggable Target Identification

Our primary approach for target identification in leukemia patients will be a functional screening of the tyrosine kinase signaling using a small molecule kinase inhibitor array. Rapid identification of activated kinase pathways is also critical to determining the unique biologic markers most useful for monitoring drug effect in each patient. Critical targets are determined by comparing the different target specificities of effective inhibitors to identify overlapping targets. Any targets of ineffective inhibitors are then subtracted. Due to the large number of inhibitors and the complexity of analysis, we have developed computer algorithms to determine which kinases are most likely involved in kinase inhibitor sensitivity. When possible, activation of signaling pathways identified by this method will be confirmed in pre-treatment samples using phospho-specific flow cytometry.

STAT5, MAP kinase, and PI3K/AKT pathways are frequently constitutively activated in acute leukemias and will be monitored with phospho-specific STAT5, p38, and AKT antibodies. Total phosphotyrosine levels will be monitored in all cases. Where antibodies suitable for flow cytometry are not available for specific targets, phosphorylation status of proteins will be monitored by immunoblot analysis. The activation status of biologic markers will be assessed immediately before therapy begins and at the two and four week time points.

2.4.2 Mechanism of Target Sensitivity - Identification of oncogenic sequence variants

We will use next generation sequencing based mutation profiling to screen for known oncogenic mutations. The current OHSU screening panel (GeneTrails) includes primers for a large number of oncogenic mutations seen in acute leukemias. Samples from all patients will also be prepared for whole exome sequencing. Germline DNA (from a skin biopsy) will be sequenced to assess germline/somatic status. We will evaluate the oncogenic potential of all mutant genes identified using a number of different methods. Initially, we will clone and express each mutant gene in Ba/F3 cells. Ba/F3 cells depend on IL-3 growth factor for viability; however, expression of a constitutively activated tyrosine kinase renders these cells capable of growth in the absence of IL-3. Activation of tyrosine kinase networks will additionally be monitored by immunoblotting of cell extracts with an antibody specific to phosphorylated tyrosine residues. We will also evaluate the capacity of mutant genes to transform other cell types using focus formation assays (NIH 3T3 cells) and colony formation assays in methylcellulose using primary murine hematopoietic cells. Some human genes do not function properly in a murine cellular setting, and in these cases, we will evaluate the mutant genes in the human cell lines TF-1 and UT-7, which are both dependent on GM-CSF in a similar manner as Ba/F3 cells require IL-3. Using these cells, pharmacokinetic studies will be performed to study drug concentration.

2.4.3 Identification of Aberrant Gene Expression

We expect that a significant proportion of inhibitor sensitive genes will be dysregulated due to other mechanisms such as overexpression, mis-splicing, or translocation, which would not be identified by either of these genomic analysis techniques. To detect these alternative oncogenic abnormalities we will perform Affymetrix Exon 1.0 microarray-based gene expression analysis. This technique involves a microarray designed to individually identify expression levels for each

exon of all genes in the genome. As such, this platform can be used to analyze global gene expression levels as well as aberrant splice variants or translocations of individual genes. To analyze this data, quality control, exploratory data analysis, model-based background correction and quantile normalization will be performed to remove systematic sources of variation. Log-transformed normalized intensities will be analyzed using linear models fit to the individual transcripts to detect alternative splicing/exon usage and modifications in transcript structure (methods developed by Dr. McWeeney at OHSU and her group). We will focus initial data analysis on genes and signaling pathways identified by functional profiling, looking for aberrant levels of expression of the genes in the affected signaling pathways.

3 STUDY POPULATION

Inclusion/exclusion criteria need not be met for the patient to sign a screening consent. Due to clinical urgency and uncertainty, pathology reports including marrow blast percentage, diagnosis, previous treatments, comorbidities, inhibitor sensitivity profile, and other requirements may not be completed or cannot be known when a patient begins the screening process. Relevant information will be gathered and data generated to determine eligibility after the patient signs the screening consent.

3.1 Inclusion Criteria

1. Participants ≥ 18 years of age with relapsed/refractory leukemia with a confirmed diagnosis of AML or ALL, who meet the following criteria: Both men and women of all races and ethnic groups will be included.

   a. Individuals aged 18-64 years with salvage* treatment failures only - defined as relapsed or refractory to after least 1 cycle of salvage therapy.

      **Given the clinical activity and use of hypomethylating agents in AML patients, initial and salvage therapy may include hypomethylating agents.*

   b. Age ≥ 65 years**: Refractory to induction chemotherapy- defined as no response to ^initial therapy or have relapsed after initial therapy.

      **Individuals aged ≥65 years, with CMML or myelodysplasia (MDS) that transform to acute leukemia while actively receiving hypomethylating agents (i.e., decitibine or azacytidine) will be considered induction failures and are thus eligible for this trial. For Ph^+ ALL, initial therapy and salvage therapy may include steroids and imatinib or dasatinib.

2. Primary patient samples must show *in vitro* kinase inhibitor sensitivity as determined by the OHSU functional kinase inhibitor screen. For OHSU patients, functional kinase inhibitor screening may be performed as part of this study or through enrollment in eIRB4422 if the identical FDA/CLIA approved assay is used and a result is available within 2 weeks of starting on study drug treatment.

3. Patients must have normal organ function as defined below:

   a. Serum creatinine < 2.0 x institutional upper limit of normal (ULN)

   b. INR < 1.5 x institutional ULN

   c. Adequate hepatic function as defined by the following criteria:

      i. Total serum bilirubin ≤1.5 x ULN, unless due to Gilbert's syndrome

ii. Alanine aminotransferase (ALT) ≤2.5 × ULN

iii. Aspartate aminotransferase (AST) ≤2.5 × ULN

4. ECOG performance status ≤ 2 (Karnofsky ≥ 60%, see Appendix A).
5. Discontinuation of anti-coagulants and anti-platelet drugs at least 7 days prior to start of study drug.
   a. Aspirin 81 mg is permitted as long as platelet count is > 50 and there is no evidence of active bleeding or coagulopathy (INR > 1.5, fibrinogen > 150).
6. No uncontrolled infections as determined by the investigator
7. No clinically significant thyroid disease (e.g. hyperthyroid/hypothyroidism)
8. No active GVHD: Patients with a history of stem cell transplant are eligible but cannot have evidence of active GVHD as determined by the investigator.
9. Must be able to take oral medication
10. Women of childbearing potential must have a negative serum or urine pregnancy test (sensitivity < 25 IU HCG/L) within 72 hours prior to the start of study drug
11. Persons of reproductive potential must agree to use an adequate method of contraception throughout treatment and for at least 4 weeks after study drug is stopped. Women of childbearing potential and men with a sexual partner of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.
12. Ability to understand and the willingness to sign a written informed consent and HIPAA document.
13. Serum Na, K, Mg, and total serum Ca or ionized Ca levels must be greater than or equal to the institutional lower limit of normal. Subjects with low K or Mg levels, total corrected serum Ca and/or ionized Ca must be replete for protocol entry.

3.2 Additional Drug specific inclusion criteria

3.2.1 Dasatinib

1. Discontinuation of any medications known to contribute significantly to the risk of QT prolongation at least 48 hours prior to start of study drug. Levaquin and Zofran are an exception. Of note, certain agents that prolong the QTc may be allowed but only after discussion with the chemotherapy pharmacist. Should the investigator believe that therapy with a potentially QT prolonging medication is vital to an individual subject's care, then additional ECGs should be done at the investigator's discretion to ensure the subject's safety.
2. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
3. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 90 days (duration of sperm turnover) for a total of 90 days post-treatment completion.

4. Azoospermic males and WOCBP, who are not heterosexually active, are exempt from contraceptive requirements. However, WOCBP must still under pregnancy testing as described in this section.
5. Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective contraception. Highly effective methods of contraception have a failure rate of <1% when used consistently and correctly.
6. At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed in Appendix B.

3.2.2 Sunitinib

None

3.2.3 Sorafenib

1. creatinine <1.5 X ULN

3.2.4 Ponatinib

1. Female and male patients who are fertile must agree to use an effective form of contraception with their sexual partners from randomization through 4 months after the end of treatment.
2. Discontinuation of any medications known to contribute significantly to the risk of QT prolongation at least 48 hours prior to start of study drug. Levaquin and Zofran are an exception. Of note, certain agents that prolong the QTc may be allowed but only after discussion with the chemotherapy pharmacist. Should the investigator believe that therapy with a potentially QT prolonging medication is vital to an individual subject's care, then additional ECGs should be done at the investigator's discretion to ensure the subject's safety.
3. Serum lipase and amylase ≤1.5 × ULN

3.2.5 Pacritinib

1. Discontinuation of any medications known to contribute significantly to the risk of QT prolongation at least 48 hours prior to start of study drug. Levaquin and Zofran are an exception. Of note, certain agents that prolong the QTc may be allowed but only after discussion with the chemotherapy pharmacist. Should the investigator believe that therapy with a potentially QT prolonging medication is vital to an individual subject's care, then additional ECGs should be done at the investigator's discretion to ensure the subject's safety.

3.2.6 Ruxolitinib

None

3.2.7 Idelalisib

None

3.3 Exclusion Criteria

1. Any leukemia treatment within 1 week (for cytotoxic therapy) and/or 5 half lives (for targeted agents) prior to starting study drug. Corticosteroids are allowable throughout the study to treat concomitant medical disorders per provider discretion. Hydroxyurea is allowed prior to enrollment and after the start of the study drug for the control of peripheral leukemic blasts in subjects with leukocytosis per physician discretion.
2. Recent uncontrolled angina, recent > NYHA class II congestive heart failure, or recent MI (within 6 months) prior to start of study treatment.
3. Diagnosed congenital long QT syndrome
4. Any recent history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsade's de pointes)
5. History of clinically significant bleeding disorder unrelated to cancer.
6. Drugs that affect the CYP3A4 system (inducers/inhibitors/substrates) are allowed but should be used with caution (see appendix D) depending on specific kinase inhibitor used. Dietary supplements will be discouraged; however, their use may be allowed on a case by case basis per the discretion of the investigator after consultation with an oncology pharmacist.
7. Uncontrolled intercurrent illness that would limit compliance with study requirements.
8. Pregnant or lactating women are excluded from this study because of possible risk to the fetus or infant
9. Known HIV-positive patients are excluded from the study because of possible risk of lethal infection when treated with marrow suppressive therapy.
10. History of hypersensitivity to any of the kinase inhibitors included in this study.

3.4 Additional Drug specific exclusion criteria

3.4.1 Dasatinib

1. Known pulmonary arterial hypertension
2. Patients may not have a clinically significant pleural or pericardial effusion.
3. Uncontrolled hypertension: inability to maintain blood pressure below the limit of 140/90 mmHg.
4. Any history of second or third degree heart block (may be eligible if the subject currently has a pacemaker)
5. Prolonged QTc interval (>450 msec for men and >470 msec for women) on pre-entry electrocardiogram.

3.4.2 Sunitinib

None

3.4.3 Sorafenib

1. Major surgery, open biopsy, or significant traumatic injury within 30 days.
2. Non-healing wound, ulcer, or bone fracture.
3. Thrombotic or embolic venous or arterial events, such as cerebrovascular accident, including transient ischemic attacks, arterial thrombosis, deep vein thrombosis and pulmonary embolism within the past 6 months.
    a. Line associated DVTs which are adequately treated (line removed and/or patient anticoagulated) are permitted.
4. Uncontrolled hypertension.
5. Active bleeding during screening.

3.4.5 Ponatinib

1. History of acute pancreatitis within 1 year of study or history of chronic pancreatitis.
2. QTC >450 msec for men and > 470 msec for women.
3. Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).
4. Any history of myocardial infarction, stroke, or revascularization.
5. Any history of venous thromboembolism including deep venous thrombosis or pulmonary embolism.
6. Unstable angina or transient ischemic attack within 6 months prior to start of study treatment.
7. Congestive heart failure within 6 months prior to enrollment, or left ventricular ejection fraction (LVEF) less than lower limit of normal per local institutional standards within 6 months prior to enrollment.
8. History of clinically significant (as determined by the treating physician) atrial arrhythmia.
9. Uncontrolled hypertension (diastolic blood pressure >90 mm Hg; systolic >140 mm Hg). Patients with hypertension should be under treatment on study entry to effect blood pressure control.
10. History of ongoing alcohol abuse.
11. Ocular toxicity present as measure during a comprehensive eye exam.

3.4.6 Pacritinib

1. Major surgery, open biopsy, or significant traumatic injury within 30 days.
2. Active bleeding during screening.
3. QTC >450 mSec for men and > 470 msec for women.
4. NYHA Class II Congestive Heart Failure (a history of CHF is allowed as long as this has resolved to < NYHA Class II within 30 days of initiation of pacritinib.

3.4.7 Ruxolitinib

1. Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or risk of

reactivation: HBV DNA and HCV RNA must be undetectable. Subjects cannot be positive for hepatitis B surface antigen (HBsAg) or anti–hepatitis B core antibody. Subjects who have positive anti-HBs as the only evidence of prior exposure may participate in the study provided that there is both 1) no known history of HBV infection, and 2) verified receipt of hepatitis B vaccine.

3.4.8 Idelalisib

1. Ongoing drug-induced liver injury, chronic active hepatitis C (HCV), chronic active hepatitis B (HBV), alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, portal hypertension, or history of autoimmune hepatitis.
2. Ongoing symptomatic pneumonitis.
3. Ongoing inflammatory bowel disease or autoimmune colitis.
4. Ongoing CMV infection, treatment, or prophylaxis within the past 28 days prior to the screening test for active CMV.
5. History of serious allergic reaction including anaphylaxis and epidermal necrolysis.

4. REGISTRATION PROCEDURES

4.1 Subject Registration

A detailed instructions for subject registration exists as a separate Study Operations Manual.

This is a phase II trial with an intention to treat all patients who are enrolled in this clinical trial. There is no randomization for treatment. Potential subjects will be seen by study investigators study as new patient, consult, or follow-up visits. Referral of potential subjects to co-investigators of this study is made as part of standard of care, with the referring physician seeking advice on the diagnosis, evaluation, and/or treatment of AML or ALL.

4.1.1 Local registration

Registrations from all consented subjects must be entered into the Knight Clinical Research Management System (CRMS). Registration of OHSU patients will include the minimum of the following:

- A completed Subject Enrollment Form
- A completed Eligibility Checklist signed by the investigator
- Signed copies of the most recently IRB-approved, informed consent form and HIPPA authorization

4.1.2 Multicenter Registration

The OHSU coordinating center study team will manage subject registration. Investigators at participating sites will identify eligible subjects and send screening materials with source documents that support eligibility to OHSU in real time and in accordance with study protocol. Designated Knight clinical staff must review and verify eligibility before the

participating site may enroll and treat its subject. The OHSU coordinating center team will verify completeness of documents, enter registration information into the Knight CRMS, and assign a study number/identifier. The coordinating center will send an email to the participating site indicating whether or not the subject is eligible, verify registration, and assign a participant number/identifier. Treatment drug selection, review of outside materials, and initiation of treatment must begin within 14 days of the baseline screening marrow. If initiation of treatment will begin after 14 days, a new baseline marrow is required.

Registration for screening will include a minimum of the following:

- A completed Subject Enrollment Form
- A completed Eligibility Checklist signed by the investigator
- Signed copies of the most recently IRB-approved, informed consent form and HIPAA authorization

Each site must maintain a screening log of all subjects who are approached to go on study, all who sign informed consents, including those who withdraw consent. The log must also document an explanation for exclusion due to screen failure. This log will be submitted to the coordinating center on a regular basis. Participating sites are required to retain, in a confidential manner, sufficient information on each subject so that the subject may be contacted should the need arise.
Registrations from all consented subjects must be entered into the Knight Clinical Research Management System (CRMS).

5. TREATMENT PLAN

5.1 Treatment Selection

Treatment selection will be based on the results of the kinase inhibitor assay and exclusion criteria. Baseline peripheral blood, bone marrow aspirate, and biopsy specimens must be taken within 14 days or less before initiating treatment. The baseline marrow biopsy is required for evaluating marrow blasts and cellularity before treatment. Drug sensitivity may be performed on the baseline bone marrow aspirate or peripheral blood specimen if circulating blasts are present. Therapeutic response will be determined using follow up bone marrow specimens noting that, when applicable, peripheral blood response will also be measured. A comparison of bone marrow blast counts between baseline and treatment samples is used to evaluate response. Samples taken anytime the patient is on active study treatment are considered treatment samples.

IC_{50} values for each kinase inhibitor will be calculated from samples and the results analyzed to determine if one of the study drugs meets criteria to be used for treatment. IC_{50} values less than 20% of the median IC_{50} value for all samples tested to date (> 500 primary leukemia samples) are considered "sensitive"; however, potentially effective drugs will generally have IC_{50} values far below 20% of the median IC_{50} for that drug. If the inhibitor screen identifies multiple treatment options and the patient meets the eligibility criteria for all, the "most effective drug" will be determined using additional sensitivity parameters including comparison with the range of results from other responders for each candidate drug, evaluation of best level of inhibition (IC_{75}, IC_{90}), and evaluation of additional curve fitting parameters (slope and area under the curve). Patients may only receive one inhibitor at a time while on study. However, if a patient

develops progression on one inhibitor (defined as a ≥ 50% increase in leukemic bone marrow blasts), he/she is eligible to re-enroll on study if, at the time of progression, another potential inhibitor is identified on repeat inhibitor plate testing he/she still satisfies the eligibility criteria. If the patient has met disease progression but is still deriving clinical benefit from the current study drug, hypomethylating agents may be added to the treatment regimen at the PI's discretion.

5.1.1 Screen Failure

A screen failure will occur if the patient sample shows no sensitivity to trial kinase inhibitors, the patient is unable to receive the selected therapy for clinical reasons, or the patient chooses not to receive treatment.

5.1.2 Non-OHSU Site Screening

For non-OHSU sites, screening samples will be sent by overnight delivery to OHSU for testing and treatment assignment. A hematopathology report describing the review of the tested/baseline marrow must also forwarded to OHSU. A formal report with screening results and treatment assignment will be forwarded to the contributing site principal investigator for inclusion in the patient's chart.

5.2 Agent Administration

Treatment will be administered on an inpatient or outpatient basis. Reported adverse events and potential risks associated with *dasatinib, sunitinib, sorafenib, ponatinib, pacritinib, ruxolitinib, and idelalisib* and are described in Section 7. Appropriate dose modifications for with *dasatinib, sunitinib, sorafenib, ponatinib, pacritinib, idelalisib and ruxolitinib* are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

Agent	Premedications; Precautions	Total Daily Dose	Route	Schedule
Dasatinib	Antacid therapy should be avoided 2 hours before and 2 hours after dasatinib ingestion	140 mg	Oral	QD
Sunitinib	Take with or without food	50 mg	oral	QD
Sorafenib	Take without food (at least 1 hour before or 2 hours after eating	800 mg	Oral	400 mg BID
Ponatinib	Take with or without food Antacid therapy should be avoided 2 hours before and 2 hours after ponatinib ingestion;	45 mg	Oral	QD
Pacritinib	Take with or without food.	400 mg	Oral	200 mg BID
Ruxolitinib	Take with or without food.	20 mg	Oral	10 mg BID
Idelalisib	Take with or without food	300 mg	Oral	150 mg BID

The patient will be asked to maintain a medication diary for each dose. The medication diary will be returned to clinic staff at the end of each course. In addition, returned oral medication will be evaluated and compared to the amount dispensed to assess compliance with regimen.

5.2.1 Supportive care or prophylactic care for Dasatinib, Sunitinib, Sorafenib, Ponatinib,

Pacritinib, Idelalisib and Ruxolitinib

Supportive care will be administered per institution guidelines. It should be noted that, although there may be a class effect for kinase inhibition, each kinase inhibitor has a unique toxicity profile.

5.2.2 Blood Products

All blood products are to be irradiated and leukocyte-reduced. Also, CMV negative patients should receive CMV negative blood products. Blood products will be administered per institutional standards as defined by the enrolling institution's blood bank.

5.2.3 Medications that inhibit Platelet Function and Anticoagulants

Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants. Subjects enrolled in this study should not take concomitant medications which durably inhibit platelet function. For such medications, a wash-out period of 7 days is required prior to starting kinase inhibitor therapy. Aspirin (up to 81 mg) is permitted as long as platelet count is > 50 and there is no evidence of active bleeding or coagulopathy (INR > 1.5, fibrinogen > 150. (Agents which inhibit platelet function transiently or inhibit coagulation by other mechanisms are restricted).

Medications which directly and durably inhibit platelet function include:
Aspirin or aspirin-containing combinations, clopidogrel, dipyridamole, tirofiban, dipyridamole, epoprostenol, eptifibatide, cilostazol, abciximab, ticlopidine, cilostazol

Medications which directly and durably inhibit anticoagulation include:
Warfarin, heparin/low molecular weight heparin (LMWH) [e.g., danaparoid, dalteparin, tinzaparin, enoxaparin] exceptions are prophylactic doses of LMWH prophylaxis to prevent catheter thrombosis and DVT. Heparin and/or TPA administered for flushes of IV lines are permitted.

5.2.4 Corticosteroids and Hydroxyurea

Corticosteroids up to and including 20 mg of prednisone (or equivalent) is allowable throughout the study. Doses > 20 mg prednisone (or equivalent) are NOT permitted unless cleared by the study PI..

Hydroxyurea is allowed prior to enrollment and after the start of the study drug for the control of peripheral leukemic blasts in subjects with leukocytosis per physician discretion.

5.2.5 Infection Prophylaxis

The general use of prophylactic antibiotics will be used per the discretion of the treating physician. Certain antibiotics may have interactions with specific kinase inhibitors and thus, this must be reviewed closely prior to study enrollment and again while the patient is on study. When necessary, dose reductions and/or prophylaxis alternatives should be made after discussions with the PI at the coordinating center and after reviewing with OHSU oncology pharmacy.

5.2.5 Treatment of Neutropenic Fever

Follow per institutional and standard of care guidelines

5.2.6 Colony Stimulating Factors

Follow per institutional and standard of care guidelines

5.2.7 Prevention of Tumor Lysis Syndrome

Prophylaxis with allopurinol 300 mg po q day is recommended to prevent the rare event of Tumor Lysis Syndrome in patients with markedly elevated numbers of circulating malignant cells. If deemed appropriate by the treating physician, rasburicase may also be use per investigator determination.

5.2.8 Management of Fluid Overload (Dasatinib patients only)

If patients experience fluid overload which often manifest as pleural effusions, the appropriate measures will be taken including:

- Chest x-ray as clinically indicated for dyspnea
- Early initiation of diuretics as clinically indicated including furosemide and/or spironolactone
- Use of steroids as clinically indicated
- Thoracentesis as clinically indicated e.g. if symptomatic pleural effusions do not respond to medical management e.g. diuretics and steroids
- Dose interruptions as outlined per protocol-this will depend on grade
- 12-lead ECG and/or echocardiogram as clinically indicated

5.2.9 Management of Skin rash

Some kinase inhibitors are associated with skin rash and/or hand-foot syndrome. Depending on severity, appropriate measures may include dose reductions and/or cessation of study drug. Depending on the kinase used, other supportive measures e.g. emollients, steroids etc. may be used per investigator judgment.

5.3 Definition of Dose-Limiting Toxicity

Toxicities will be graded in severity according to the guidelines outlined in the NCI-CTCAE v4.03. Dose-limiting hematologic and non-hematologic toxicities will be defined differently. In order to be declared a dose-limiting toxicity, an adverse experience must be determined related (definitely, probably, or possibly) to study drug. All DLTs must be reported to the coordinating center within 24 hours of occurrence. Only prolonged Grade 4 hematologic toxicities and ≥ Grade 3 non-hematologic toxicities will be reported. It should be noted that some study drugs have unique toxicities and therefore some Grade 2 non-hematologic related toxicities may be counted as a DLT. These are outlined below:

5.3.1 Hematologic dose-limiting toxicity

Any prolonged Grade ≥4 neutropenia or thrombocytopenia lasting 14 or more days, or as defined by NCI CTCAE v 4.03, leukemia-specific criteria-marrow cellularity <5% on Day 28 or later from the start of study drug without evidence of leukemia) at least 42 days after the initiation of Cycle 1 therapy. Leukemia-specific grading should be used for cytopenias (based on percentage decrease from baseline: >75% = Grade 4)- considered by the investigator to be related to study drug. It should be noted that many patients with leukemia have significant thrombocytopenia, anemia, and neutropenia from their disease and thus, if hematologic toxicity is determined to be from disease (opposed to study drug toxicity) then this will not be considered to be a DLT.

5.3.2 Non-hematologic dose-limiting toxicity

Non-hematologic DLTs will be defined as any ≥ Grade 3 non-hematologic toxicity considered by the investigator to be related to study drug. Certain drugs may require dose interruptions and/or dose reductions based on specific toxicities that may be Grade 2 as follows:
In addition to the criteria defined above, reportable drug-specific significant DLTs that require dose interruption and modification are outlined below:

5.3.3 Drug Specific DLTs

5.3.3.1 Dasatinib
- QTc >480 msec for men and >500 msec for women

5.3.3.2 Sunitinib
- Grade ≥2 symptomatic or persistent hypertension (HTN) or diastolic BP > 110.

5.3.3.3 Sorafenib
- Grade >2 Hand-Foot Skin Toxicity.
- Grade ≥2 symptomatic or persistent hypertension (HTN) or diastolic BP > 110.

5.3.3.4 Ponatinib
- Grade ≥2 transaminitis
- Grade ≥2 transaminitis with concurrent Grade ≥ 2 hyperbilirubinemia
- Grade ≥2 radiologic evidence of pancreatitis

5.3.3.5 Pacritinib
- Grade >3 Diarrhea
- Grade >2 Dizziness
- QTc >480 msec for men and >500 msec for women

5.3.3.6 Ruxolitinib
- Grade >3 or 4 hemorrhage event.

5.3.3.7 Idelalisib
- Stevens Johnson Syndrome or toxic epidermal necrolysis of any grade
- Pneumocystis (PCP) pneumonia of any grade

- Clinically significant (unequivocal) CMV infection of any grade
- ≥ grade 2 diarrhea
- ≥ grade 3 transaminitis
- ≥ grade 2 pneumonitis

5.3.4 Non-reportable, insignificant toxicities (not defined as DLT)

- Grade 2-3 nausea, diarrhea, dehydration, or vomiting lasting <48 hours that in the opinion of the investigator results from inadequate compliance with supportive care measures
- Grade 3 acidosis or alkalosis that which responds to medical intervention by returning to ≤ Grade 2 within 48 hours
- Grade 2-3 elevation of liver function tests (LFTs) without associated clinical symptoms, lasting for ≤7 days in duration
- Grade 2-3 elevation of amylase without associated clinical symptoms
- Grade 2-3 hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hypophosphatemia and which responds to medical intervention
- Grade 2 or 3 weight loss
- Grade 2-3 infection that is controlled on antimicrobial therapy
- Grade 2-3 fatigue lasting ≤7 days in duration
- Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Cytochrome P450 inducers and inhibitors

Because there is a potential for interaction of study agent(s) with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The principal investigator should be alerted if the subject is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes (Refer to Appendix C for a list of inducers and inhibitors).

Supportive care with be administered per institutional guidelines. Of note, some supportive care medications, for example, antibiotics and antifungals that are routinely used in the care of acute leukemia patients may involve the CYP3A4 metabolism as outlined below. These agents may be used after documented consultation with an oncology pharmacist. See also Appendix B for lists of medications that act on CYP and PGP substrates.

Drugs that induce CYP3A4 activity may decrease kinase inhibitor plasma concentrations. In patients in whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be used. Likewise exposure to a CYP3A4 inhibitor may increase exposure to certain kinase inhibitors. A summary of dose modifications for each respective study agent when administerd in combination with CYP3A4 inhibitors is shown in **Table 1.**

Table 1. Study agent dose adjustments when used concomitantly with CYP3A4 inhibitor		
Target Dose	**Dose with Moderate**	**Dose with Strong Inhibitor**

	Inhibitor	
Dasatinib		
100 mg daily	50 mg daily	20 mg daily
140 mg daily	70 mg daily	40 mg daily
Sunitinib		
50 mg daily	No adjustment	37.5 mg daily
Sorafenib		
800 mg daily	No dose reduction	No dose reduction
Ponatinib		
45 mg daily	No adjustment	30 mg daily
Pacritinib		
400 mg	No dose reduction	No dose reduction
Ruxolitinib		
20 mg	15 mg daily	10 mg daily
Idelalisib		
300 mg	No dose reduction	No dose reduction

Dasatinib: Dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and drugs that inhibit CYP3A4 may increase exposure to certain kinase inhibitors. Close monitoring for toxicity and a dose reduction should be considered as listed in the tables below if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

Sunitinib: If an inducer is required for patient care sunitinib may be increased to 62.5 mg daily.

Sorafenib: CYP3A4 inducers should be avoided when prescribed sorafenib.

Ponatinib: If ponatinib must be administered with a CYP3A4 inducer, a dose increase in kinase inhibitor should be considered.

Pacritinib: No dose adjustments of pacritinib are needed when used concomitantly with moderate or strong CYP 3A4 inhibitors.

Ruxolitinib: When possible, CYP3A4 inhibitors should be avoided as they may have effects on ruxolitinib levels, and alternative therapies should be sought if available. Drugs that are weak inhibitors of CYP3A4 or are CYP 3A4 inducers require no dose adjustment for the starting dose but the investigators may choose to adjust the dose at their discretion.

For strong CYP3A4 Inhibitors or Fluconazole, ruxolitinib dose should be reduced, interrupted, or discontinued as recommended. Avoid use of ruxolitinib with fluconazole doses greater than 200 mg.

Idelalisib: No dose adjustments are needed. However, the following should be considered:
Idelalisib adjustments: idelalisib is a strong CYP3A inhibitor at the registered dose of 150 mg twice daily, but is expected to be a moderate CYP3A inhibitor at the lower dose of 50 mg twice daily. The metabolite of idelalisib, GS-563117, is a competitive and time dependent inhibitor of CYP3A; accordingly coadministration of idelalisib 150 mg twice daily with midazolam, a probe CYP3A substrate, resulted in an approximately 5-fold increase in midazolam systemic exposure (AUC). Coadministration of CYP3A substrates with idelalisib may result in an increase in their systemic exposures (eg, certain antiarrhythmics, calcium channel blockers, benzodiazepines, HMG-CoA reductase inhibitors, phosphodiesterase-5 [PDE5] inhibitors, and warfarin).

Particular caution is recommended during coadministration of idelalisib with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, including narrow therapeutic index CYP3A substrates (eg, alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine, astemizole, terfenadine) with idelalisib.

The investigator should review the prescribing information of the concomitant medication for guidance on coadministration with a CYP3A inhibitor. In addition, data suggest that when idelalisib is administered with potent inducers of CYP3A (such as rifampin) that idelalisib exposure is significantly reduced. As such, potent inducers or inhibitors of CYP3A should be avoided. However, no specific dose modifications are recommended for moderate or strong inhibitors and agents undergoing CYP3A may be allowed after consultation with the oncology pharmacist.

Dose adjustments are based on estimates with inhibitors or inducers of similar strength. Doses may be increased or decreased based upon individual patient tolerance. Subjects should be advised not to consume substantial quantities of grapefruit juice and other citrus products should be approved by the treatment team prior to use.

5.4.2 Gastro-intestinal -anti-emetics, anti-diarrheal agents and acid suppressive therapy (antacids, H2 blockers, proton pump inhibitors)

Study participants may receive anti-emetic therapy as needed during their treatment which may include ondansteron, prochlorperazine, haloperidol and lorazepam. Some kinase inhibitors have been associated with diarrhea and patients will be administered anti-diarrheals per investigator's discretion. First line agents include loperamide.

Nonclinical data demonstrates that the solubility of certain kinase inhibitors are pH dependent. H2 blockers or proton pump inhibitors will be avoided if possible in subjects receiving dasatinib, or ponatinib. The use of antacids should be considered in place of H_2 blockers or proton pump inhibitors in patients receiving kinase inhibitor therapy. However, if antacid therapy is needed, simultaneous administration should be avoided and the antacid dose should be administered 2 hours after the dose of inhibitor. Sorafenib, sunitinib, ruxolitinib and idelalisib may be taken without regard to the above acid reducing agents.

5.5 Duration of Treatment

Treatment will continue uninterrupted for a minimum of one treatment cycle (28 days), until treatment is approved for this indication or until one of the following criteria applies**:**

- Disease progression (defined as a ≥ 50% increase in leukemic bone marrow blasts)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events(s)
- Subject decides to withdraw from the study
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator
- For any reason, at the Sponsor or Investigator's discretion

5.6 Duration of Follow-up

All patients enrolled in the trial, regardless of the number of cycles completed, will be followed for disease progression and survival status. Subject will be followed by review of the medical record until death. Subjects removed from study for unacceptable adverse event(s) will be followed until death. If a subject withdraws consent for further treatment, the subject's willingness to continue in the follow-up phase of the study will be determined.

5.7 Criteria for Removal from Study

Subjects will be removed from study when any of the criteria listed in Section 10.4 applies. The reason for study removal and the date the subject was removed must be documented in the Case Report Form.

5.8 Study Discontinuation

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Reasons for terminating the study may include the following:

- Toxicity
- Incomplete or inaccurate data recording
- Lack of adherence to the protocol or applicable regulatory guidelines in the conduct of the study

6. DOSING DELAYS/DOSE MODIFICATIONS

Because this study is designed to test the screening assay's ability to predict effective therapies, dose delays and modifications are limited. Study drugs should be maintained at their highest doses to maximize the potential for a treatment effect. However, a study drug may be held for up to 5 days after which study drug will be restarted for a full 28 day cycle. If holding drug, the investigator should assess AEs daily to determine if subject is appropriate for re-initiation of treatment. If a treatment delay is longer than 5 days the subject will be removed from the study. At that point, if appropriate, they may be rescreened.

Study drug should be held for a maximum duration of 5 days in the presence of a DLT (defined in section 5.3):

- Grade ≥ 3 drug-related non-hematologic toxicity except for the exceptions listed above and prolonged Grade ≥ 4 hematologic toxicity until the toxicity resolves or returns to Grade 1 for non-hematologic toxicity,
- Grade 2 for hematologic toxicity, or back to baseline.

If the toxicity does not resolve after holding drug for up to 5 days then the subject will be removed from the study. In the event of such toxicity, study drug will be re-administered at lower dose levels noting that dose reductions will only be performed for non-hematologic toxicity. Dose interruption and/or dose reduction will vary depending on the drug and the toxicity. This schema is outlined for each specific drug in section 6.1. Interruption and/or dose reduction of study drug(s) should be assessed on a case by case basis based on the study drug's probable causality of the toxicity. The coordinating center must be notified regarding any dose interruption or dose reduction within 24 hours of occurrence.

As noted above, during dose interruptions, hydroxyurea (HU) or corticosteroids (prednisone > 20 mg) may be used per the discretion of the treating physician. However, HU must be discontinued at re-initiation of study treatment.

For hematologic toxicity, the use of hematopoietic growth factors, such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, is permitted on study; these agents may be used to support blood counts as clinically indicated to minimize treatment interruptions.

6.1 Dose Modifications for Dasatinib

6.1.1 Dasatinib Dose Modification for Hematologic Toxicity

No dose reductions are to be performed as patients are expected to have pancytopenia requiring transfusions. The exception is drug related toxicity that satisfy the DLT criteria as defined in section 5.3.

6.1.2 Dasatinib Dose Modifications for Non - Hematologic Toxicity

Grade	Dose Modification
1	No dose modification
3	Stop dasatinib hold up to 5 days When AE returns to < grade 1 or baseline, resume dasatinib at 100 mg QD. If after 7 days, no additional toxicity is seen, increase to 140 mg QD (original dose). If toxicity recurs, then dasatinib should be dose reduced to 100 mg QD and the subject should be continued on this dose for the duration of the study. If the AE recurs despite dose reduction, then the patient should be taken off study.
Grade 4	Stop Dasatinib, hold up to 5 days When AE returns to < grade 1 or baseline, resume dasatinib at 100 mg QD. Subject will continue at this dose for the duration of the study If AE recurs, remove subject from study

6.1.3 Dasatinib Dose Modification for QT Prolongation

If QTc > 480 msec for men or > 500 msec for women:

1. Stop dasatinib for up to 5 days

2. Perform an analysis of serum electrolytes (including potassium and magnesium) and correct to WNL if required.
3. Review concomitant medications for drug interactions
4. Resume dasatinib at prior dose if QTc returns to < 450 msec for men and < 470 for women and to within 20 msec of baseline.
5. If QTc is between 450 msec and 480 msec for men or between 470 msec and 500 msec for women after 7 days reduce the dose to 100 mg daily
6. If following dose-reduction, the QTc returns to >480 msec for men or > 500 msec for women, dasatinib should be discontinued
7. An ECG should be repeated 7 days after any dose adjustment.

6.2 Dose Modifications for Sunitinib

6.2.1 Sunitinib Dose Modifications for Hematologic Toxicity

No dose reductions are to be performed as patients are expected to have pancytopenia requiring transfusions. The exception is drug related toxicity that satisfy the hematologic DLT criteria as defined in section 5.3.

6.2.2 Sunitinib Dose Modifications for Non-Hematologic Toxicity

Grade	Dose Modification
1 or 2	No dose modification
3 -4	Stop sunitinib Can hold up to 5 days When AE returns to ≤ grade 1 or baseline, resume sunitinib at dose -1 (37.5 mg QD]). If tolerated for 7 days, dose can be increased to original dose (50 mg QD). If toxicity recurs at this dose, dose will be reduced to 37.5 mg QD and patient will continue on this dose for the duration of the study. If toxicity recurs after dose reduction, patient will be removed from the study

6.2.3 Sunitinib Dose Modification for Cardiac Toxicity

1. For Grade 3 systolic (LV) dysfunction hold sunitinib for up to 5 days.
2. If toxicity resolves to < Grade 3, restart sunitinib at 37.5 mg once daily.
3. If no recurrence of cardiac toxicity after 7 days, increase to 50 mg once daily. If no toxicity is seen, subject should be maintained at this dose.
4. If toxicity recurs at 50 mg dose, hold sunitinib up to 5 days and if toxicity resolves to < grade 3, restart sunitinib at 37.5 mg daily and maintain this dose for the remainder of the study.
5. If toxicity recurs at 37.5 mg at any time on the study, discontinue sunitinib and remove patient from the study.

6.2.4 Sunitinib Dose Modification for Hypertension

Grade (CTCAE v4.0)	Antihypertensive Therapy	Blood Pressure Monitoring	Sunitinib Dose
Grade 2 (symptomatic)	Initiate monotherapy (suggest dihydropyridine calcium-channel blocker)	Increase frequency and monitor (by health professional) every 2 days until stabilized	No change

Grade 2 (symptomatic/ persistent) OR Diastolic BP > 110 mm Hg OR Grade 3	Add agent(s): Ca^{++} channel blocker (if not already used), K+ channel opener (angiotensin blockers), beta-blocker, thiazide diuretic	Increase frequency and monitor every 2 days until stabilized; continue every other day monitoring to stabilization after dosing restarted.	Hold* sunitinib for up to 5 days until symptoms resolve and/or diastolic BP < 100 mm/Hg. Resume sunitinib treatment at 37.5 mg daily. If tolerated for 7 days (no > grade 2 HTN), increase to original/starting dose. If recurs at original dose despite anti-HTN agents, remove from protocol
Grade 4			Discontinue sunitinib

6.2.5 Sunitinib Dose Modification for Proteinuria

1. For Grade 3 proteinuria, interrupt sunitinib treatment for up to 5 days.
2. If proteinuria resolves to < Grade 3, restart sunitinib at 37.5 mg daily.
3. If toxicity recurs at 50 mg daily, interrupt sunitinib treatment for up to 75days and if proteinuria resolves to < Grade 3, restart sunitinib at 37.5 mg daily.
4. If toxicity recurs at 37.5 mg, stop sunitinib and remove from the study.

6.3 Dose Modifications for Sorafenib

6.3.1 Sorafenib Dose Modifications for Hematologic Toxicity

No specific dose reductions are to be performed as patients are expected to have pancytopenia requiring transfusions. The exception is drug related toxicity that satisfy the hematologic DLT criteria as defined in section 5.3.

6.3.2 Sorafenib Dose Modifications for Non-hematological Toxicity

Toxicity	Grade 1	Grade 2	Grade 3*	Grade 4*
Non-hematologic Note: Specific dose modifications for hypertension and hand-foot skin reactions	Continue at the same dose level.	Continue at the same dose level.	Withhold dose for up to 5 days until toxicity is grade ≤1, then resume treatment at a reduced dose of 400 mg p.o. qd. If patient tolerates this dose for 7 days, he/she can receive the original treatment dose (400 mg BID). If the subject experiences another toxicity despite dose reduction (400 mg QD), he/she will be removed from the study.	Withhold dose until toxicity is grade ≤1, then reduce dose to 400 mg qd and resume treatment, or discontinue at the discretion of the principal investigator.

6.3.3 Sorafenib Dose Modifications for Toxicity related to Hypertension

Hypertension is a known and potentially serious adverse event associated with Sorafenib treatment. Dose modifications are based on average daily blood pressure. Only grade 3 hypertension will be captured for study purposes.

Grade	Antihypertensive Therapy	Blood Pressure Monitoring	Sorafenib Dose
Grade 1	None	Routine	No change
Grade 2 (asymptomatic)	Initiate monotherapy (suggest dihydropyridine calcium-channel blocker)	Increase frequency and monitor	No change
Grade 2 (symptomatic/ persistent) **OR** Diastolic BP > 110 mm Hg **OR** Grade 3	Add agent(s): Ca^{++} channel blocker (if not already used), K+ channel opener (angiotensin blockers), beta-blocker, thiazide diuretic	Continue inpatient monitoring per ward guidelines	**Hold* Sorafenib for up to 5 days until symptoms resolve and diastolic BP < 100 mm/Hg.** Restart at 400 mg daily. If tolerated for 7 days (no > grade 2 HTN), increase to original/starting dose (800 mg BID). If this recurs at original dose, decrease to or 400 mg QD. If toxicity recurs, then patient will stay on the reduced dose (400 mg QD) for the duration of the study. If the toxicity recurs on the lower dose (400 mg QD) despite anti-HTN agents, remove from protocol

6.3.4 Sorafinib Dose Modifications for Hand-Foot Skin Reaction

If Grade 2 or 3:
1. Decrease sorafenib to 400 mg daily
2. If toxicity does not return to grade 0-1 despite dose reduction, interrupt sorafenib treatment for up to 5 days, until toxicity has resolved to grade 0–1
3. If no further toxicity is seen after 5 days can restart, if toxicity is maintained at Gr. 0-1 for another 7 days can increase dose again to full dose.
4. If toxicity recurs, stop sorafenib and remove subject from study.

6.4 Dose Modifications of Ponatinib

6.4.1 Ponatinib Dose Modifications for Hematologic Toxicity

No dose reductions are to be performed as patients are expected to have pancytopenia requiring transfusions. The exception is drug related toxicity that satisfy the DLT criteria as defined in section 5.3.

6.4.2 Ponatinib Dose Modifications for Non-Hematologic Adverse Reactions

If a serious non-hematologic adverse reaction occurs, modify the dose or interrupt treatment. Do not restart ponatinib in patients with arterial or venous occlusive reactions unless the potential benefit outweighs the risk of recurrent arterial or venous occlusions and the patient has no other treatment options. For serious reactions other than arterial or venous occlusion, do not restart ponatinib until the serious event has resolved or the potential benefit of resuming therapy is judged to outweigh the risk. These scenarios are outlined below.

Grade 1 or transient Grade 2	No intervention
Grade 2 lasting ≥7 days with optimal care (except hepatic toxicity and pancreatitis recommendations described in the tables below)	Hold ponatinib for up to 5 days; Resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg: Hold ponatinib for up to 5 days; Resume at 30 mg after recovery to ≤ grade 1
Grade 3 or 4	Hold ponatinib for up to 5 days; When AE returns to ≤ grade 1 or baseline, resume at 30 mg after recovery to ≤ grade 1. If toxicity recurs, then ponatinib should be dose reduced to 30 mg QD and the subject should be continued on this dose for the duration of the study. If the AE recurs despite dose reduction, then the patient should be taken off study.

6.4.3 Ponatinib Dose Modifications for Hepatic Toxicity

Elevation of liver transaminase > 3x ULN* (Grade 2 or higher)	Occurrence at 45 mg: Interrupt ponatinib for up to 5 days and monitor hepatic function Resume ponatinib at 30 mg after recovery to ≤ Grade 1 (< 3 × ULN) Resume ponatinib at 30 mg after recovery to ≤ Grade 1 (< 3 × ULN). Continue on this dose for the remainder of the study. If toxicity recurs at 30 mg: Remove from study
Elevation of AST or ALT ≥ 3 x ULN concurrent with a Grade 2 elevation of bilirubin > 2 x ULN and alkaline phosphatase < 2 x ULN	Discontinue ponatinib
*ULN = Upper Limit of Normal for the lab	

6.4.4 Ponatinib Dose Modifications for Pancreatitis and Elevation of Lipase

Asymptomatic Grade 3 or 4 elevation of lipase (> 2 x ULN*) or asymptomatic radiologic pancreatitis (Grade 2 pancreatitis)	Interrupt Ponatinib for up to 5 days and resume at 30 mg after recovery to ≤ Grade 1 (< 1.5 x ULN) Occurrence at 30 mg: Discontinue ponatinib, remove from study
Symptomatic Grade 3 pancreatitis	Occurrence at 45 mg: Interrupt ponatinib for up to 5 days and resume at 30 mg after complete resolution of symptoms and after recovery of lipase elevation to ≤ Grade 1 If toxicity does not occur after 7 days of treatment at this dose, restart ponatinib at 45 mg once daily. If toxicity recurs, interrupt drug for up to 7 days. Resume ponatinib at 30 mg after recovery to ≤ Grade 1 (< 3 × ULN). Continue on this dose for the remainder of the study. Occurrence at 30 mg: Discontinue ponatinib, remove from study

Grade 4 symptomatic pancreatitis	Discontinue ponatinib and remove from study

6.5 Dose Modifications of Pacritinib

In addition to drug related toxicity that satisfy the DLT criteria as defined in section 5.3, specific dose adjustments/interruptions may be warranted. Available doses for this study are 200 mg BID (starting dose) and 200 mg QD (dose level -1). No further dose reductions will be allowed.

6.5.1 Pactritinib Dose Modifications for Hematologic Toxicity

In addition to drug related toxicity that satisfy the DLT criteria as defined in section 5.3, specific dose adjustments/interruptions may be warranted.

Treatment Toxicity and Dosage Management: Hematologic Toxicities and Related Complications	
CTCAE Toxicity Grade	**Management/Action**
Grade 4 hemorrhage (life-threatening consequences; urgent intervention indicated)	Discontinue pacritinib permanently

6.5.2 Pacritinib Dose Modifications for Non-hematologic Toxicities

Event	**Grade**	**Management/action**
Any non-hematologic event that was related to the study drug	1 or 2	No change
	3	Hold treatment. Treatment may resume if toxicity is resolved to grade ≤1 or returned to baseline. Starting dose may be at the same level if the toxicity resolves within 7 days or decreased by 25% daily at the discretion of the investigator after discussion with the sponsor. Toxicity lasting >7 days requires doses reduction by ≥25% daily at the discretion of the investigator after discussion with the sponsor. Dose reductions were accomplished using available strengths of the study drug, rounding down if necessary.
	4	Hold treatment. Treatment may resume if toxicity is resolved to grade ≤1 or returned to baseline at the discretion of the investigator after discussion with the sponsor. A 25% daily dose decrease is required at treatment resumption. Dose reductions were accomplished using available strengths of the study drug, rounding down if necessary.

6.5.3 Pacritinib Dose Modifications for QTc Interval Prolongations and Reduction in Ejection Fraction

Treatment Toxicity and Dosage Management: QTc Interval Prolongation and Reduction in Ejection Fraction	
CTCAE Toxicity Grade	**Management/Action**
1	No change.
2 (first occurrence)	▪ Hold treatment for up to 5 days. If toxicity resolves to grade ≤1 within 5 days, treatment may be resumed at the same level or the next lower dosage (200 mg QD). ▪ Toxicity that does not resolve to grade ≤1 within 5 days requires treatment discontinuation.
2 (second occurrence)	Discontinue treatment.
3 and 4	Discontinue treatment.

Discontinue treatment with pacritinib for all other grade 4 cardiac toxicities.

6.5.4 Pacritinib Dose Modifications for Diarrhea

Treatment Toxicity and Dosage Management: Diarrhea	
CTCAE Toxicity Grade	**Management/Action**
1 or 2	No change.
3	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤1 or to the baseline grade within 5 days, treatment may be resumed at the same level or the next lower dosage (200 mg QD). o If the toxicity recurs after restart at the same dosage level, treatment may only be resumed at the next lower dosage level (200 mg). o If the toxicity resolves to grade ≤1 or to the baseline grade after more than 5 days, treatment may be resumed only at the next lower dosage level (200 mg QD). o If the toxicity recurs after restart at the lower dosage level (00 mg QD), pacritinib treatment must be discontinued.
4	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤1 or to the baseline grade within 5 days, treatment may be resumed, but dosage will be reduced by 1 dosage level (200 mg QD) from the level at which the toxicity was observed.

6.5 Dose Modifications of Ruxolitinib

6.5.1 Dose Modifications of Ruxolitinib for Hematologic Toxicity

No dose reductions are to be performed as patients are expected to have pancytopenia requiring transfusions. In addition to drug related toxicity that satisfy the DLT criteria as defined in section 5.3, specific dose adjustments/interruptions may be warranted.

6.5.2 Dose Modifications for Non-Hematologic Adverse Reactions

The following dose adjustments will be made for patients with a GFR < 60.

- CrCl 15 to 59 mL/minute, 5 mg PO BID

Toxicity	Maximum Dose When Restarting Ruxolitinib Treatment
Ongoing (lasting > 24 hours) Grade 3 or higher hemorrhage event.	First occurrence: hold for up to 5 days until Grade 1 or baseline and resume at 15 mg twice daily Second occurrence: hold for up to 5 days until Grade 1 or baseline and resume at 10 mg twice daily

There are no additional ruxolitinib specific drug interruption/hold criteria for non-hematologic toxicity. The exception is drug related toxicity that satisfy the DLT criteria as defined in section 5.3.

6.6 Dose Modifications of Idelalisib

6.6.1 Idelalisib Dose Modifications for Hematologic Toxicity

No dose reductions are to be performed as patients are expected to have pancytopenia requiring transfusions. The exception is drug related neutropenia.

6.6.2 Idelalisib Dose Modifications for Non-Hematologic Adverse Reactions

Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (any grade)	Discontinue idelalisib. Interrupt any co-administered medications potentially associated with SJS or TEN. Institute systemic immunosuppression per institutional standards.
Bowel perforation	Discontinue idelalisib.
Diarrhea	For Grade 2, withhold idelalisib up to 5 days until Grade ≤ 1. Provide anti-diarrheal (e.g., loperamide). Resume idelalisib at previous dose level. If rechallenge results in recurrence, resume at lower dose level (100 mg po BID). Consider addition of anti-inflammatory (e.g., sulfasalazine, budesonide). If toxicity persists or recurs following dose reduction discontinue idelalisib. For Grade 3 or 4, Withhold study drug for up to 5 days. Rule out infectious etiology including CMV. Consider anti-diarrheal (e.g., loperamide) and/or addition of anti-inflammatory agent (e.g., sulfasalazine, budesonide). At Grade ≤1, may resume at lower dose level (100 mg po BID) or discontinue study drug at investigator discretion. If toxicity persists or recurs following a dose reduction permanently discontinue idelalisib per provider discretion.
Pneumonitis	For Grade 3 or higher, withhold study drug up and discontinue permanently. Institute systemic corticosteroids.

Pneumocystis pneumonia (any grade)	Discontinue idelalisib.
Unequivocal CMV infection (any grade)	Discontinue idelalisib and undergo effective antiviral treatment according to established clinical guidelines.
Transaminase elevations (Grade 3 or 4)	Grade 3 or 4 elevations can be managed by temporarily withholding idelalisib (up to 5 days).

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting. Any grade 3 toxicities or higher will be tracked as outlined in the table below.

7.1 Limited Collection of Non-Serious Adverse Events

Many AEs are expected during induction chemotherapy with high rates especially of hematologic and infectious complications and so a limited number of AE will be collected for this trial. The chart below shows which AEs will be collected and tracked. The principal investigator will be responsible for determining the expectedness/relationship of the AE to the study drug as appropriate for grade 3/4 AEs. AE collection will begin on the first day of the start of the induction chemotherapy and continue until 30 days post last dose of study drug.

ADVERSE EVENT TRACKING REQUIREMENTS				
Grade of adverse Event	Unexpected in Induction Setting	Expected in Induction setting	Unrelated to study drugs	Related to Study Drugs
Grade 1	Not tracked	Not tracked	Not tracked	Not tracked
Grade 2	Not tracked	Not Tracked	Not tracked	Not tracked
Grade 3	Tracked and reportable	Tracked and reportable	Tracked and reportable	Tracked and reportable
Grade 4	Tracked and reportable	Tracked and reportable	Tracked and reportable	Tracked and reportable
Grade 5	Tracked and reportable	Tracked and reportable	Tracked and reportable	Tracked and reportable
Serious Adverse Events	Tracked and reported	Tracked and reported	Tracked and reported	Tracked and reported
Note: would track adverse events that would lead to dose reductions including cardiac toxicities,				

hypertension, pancreatitis, LFT elevation and QTc prolongation as well as hand-skin foot rash

7.2 Adverse Events and Potential Risks List(s)

Complete details are available in the prescribing information for each drug used in this study. Pacritinib details are available in the Investigator's Brochure.

Adverse Events of Special Interest (AESIs) are listed below.

7.2.1 Ponatinib

Adverse Events of Special Interest (AESIs): Vascular occlusive events have been identified as AESIs for ponatinib. These include arterial and venous thrombotic and occlusive adverse events that meet the criteria for SAEs (cross-refer to the section where the serious criteria are described and defined) and those adverse events that do not meet the SAE criteria.

AESIs require ongoing monitoring by investigators and rapid identification and communication by the investigator to the study sponsor. All AESIs, whether SAEs or not, must be reported within 2 business days of the study sponsor awareness to ARIAD. ARIAD has determined that the events listed below (whether considered serious or non-serious by investigators) should be considered AESIs:

- **Myocardial infarction:** The Third Universal Definition of Myocardial Infarction (28) is used to define MI
- **Angina** (newly diagnosed or worsening of existing angina or unstable angina)
- **Coronary artery disease (CAD)** (newly diagnosed or worsening of existing CAD) or symptoms that may reflect cardiovascular disease (28)
- **Cerebrovascular ischemic disease** including ischemic or hemorrhagic stroke, vascular stenosis, transient ischemic accident (TIA), cerebrovascular occlusive disease documented on diagnostic neuroimaging, or symptoms that may reflect cerebrovascular disease(29)
- **New onset or worsening of peripheral artery occlusive disease** (e.g., renal artery, mesenteric artery, femoral artery) or symptoms that may reflect peripheral vascular disease
- **Retinal vascular thrombosis**, both venous and arterial
- **Venous thromboembolism** where significant compromise of organ function or other significant consequences could result (e.g., pulmonary embolism, portal vein thrombosis, renal vein thrombosis) or symptoms that may reflect venous thrombosis

7.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Expectedness: Adverse Events can be 'Unexpected' or 'Expected' (see Section 7.1 above for expected AEs) based on available safety data. *Define any events of interest that may require special reporting.*

Attribution of the AE:

- Definite – the AE *is clearly related* to the study treatment.
- Possible – the AE *may be related* to the study treatment.
- Unrelated – the AE *is clearly NOT related* to the study treatment.

7.3.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study. Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

7.3.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. 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.
- Events **not** considered to be serious adverse events are hospitalizations for:
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition, or for elective procedures.
- Elective or pre-planned treatment for a pre-existing condition that did not worsen.
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission.
- Respite care.

7.3 OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems (UP) and Adverse Events (AE) will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site

Fatal and life-threatening events must be reported to OHSU IRB within 7 calendar days after the PI learns of the event. If any of these require a change (as determined by the PI or the IRB) to the protocol or consent form, the PI will make those changes promptly and submit the revised documents to the OHSU IRB.

All other UP reports will be submitted to OHSU IRB no later than 15 calendar days of notification of the event. If the event requires changes as determined by the PI or the IRB) to the protocol or consent form, the PI will make the changes promptly and submit the revised documents to the IRB. UP and AE reports are submitted through OHSU e-IRB and will be reviewed by OHSU IRB.

7.4 Central Reporting of Adverse Events for Multicenter Studies

The SAE/UP reporting for multicenter investigator initiated clinical trials will follow the guidelines outlined in the OHSU Knight Cancer Institute Multi-Center Investigator Initiated Trials Coordinating Center Operations Manual.

A participating site must report an SAE to the to the institution's local IRB for action as required, as well as to the OHSU coordinating center study team by phone, fax, or email within 24 hours of learning of the event. The participating center will send the coordinating center materials regarding the SAE

The OHSU coordinating center study team will review and submit SAEs to the FDA, OHSU IRB, and any other required contacts as required by the Knight Data Safety Monitoring Plan. The principal investigator at the Coordinating Center is responsible for distributing IND and/or IDE Action Letters or Safety Reports, as applicable, to participating institutions for review and submission to their institution's local IRB.

7.5 MedWatch Reporting

For this investigator-initiated study, the investigator is the study sponsor. The investigator/sponsor is required to report adverse experiences to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent. Adverse experiences to be reported include any unexpected (not listed in the package label), serious adverse experiences with a suspected association to the study drug.

Adverse events that occur during clinical studies are to be reported to FDA as specified in the investigational new drug/biologic regulations using the FDA 3500A Mandatory Reporting form, which is available online.

This is available as a .pdf document for printing.

When the serious adverse event is reported to the FDA, copies of the MedWatch 3500A form and supporting materials will be submitted to the OHSU Knight Cancer Institute and the IRB. A

copy of the MedWatch 3500A form and supporting materials will be kept on file in the study regulatory binder.

7.6 Sponsor or Additional Reporting Requirements

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

All events reported to the FDA will also be reported to drug manufacturer representative within 24 hours of reporting. A copy of the FDA report will also be faxed to the drug manufacturer representative.

7.6.1 Reporting to ARIAD

All serious adverse events, whether "reportable" as defined in this protocol or not, must be reported to ARIAD. All expedited (7/15 day) reports will be sent to ARIAD simultaneously or within 24 hours of study sponsor's submission to the competent authorities. Non-expedited SAE reports (except for AESIs) can be batched by the study sponsor and sent to ARIAD on a monthly basis. Also, any event of a vascular occlusive nature, either serious or non-serious, must be reported to ARIAD **within 2 business days** of the study sponsor's awareness.
The study PI or designee is responsible for faxing SAE reports to ARIAD Pharmaceuticals, Inc., at 1 (888) 472-7965. Reports may be emailed if fax is not available to ARIADPost-PVGSM@ppdi.com.

7.6.2 Reporting to Bayer

Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports to the designated person. An isolated laboratory abnormality that is assigned grade 4, according to CTC definition, is not reportable as an SAE; unless the investigator assesses that the event meets standard ICH criteria for an SAE. CTC grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.

When required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

All serious adverse events should be reported to Bayer within 24 hours. In the event of such an event, the investigator should refer to the Pharmacovigilance section of the contract for reporting

procedures.

The Investigator may report serious adverse drug reactions (SADRs) using either:

- An ADEERS form (Adverse Event Expedited Reporting System) available at http://ctep.cancer.gov/reporting/adeers.html, OR
- A MedWatch form available at http://www.fda.gov/medwatch/

All reports shall be sent electronically to:

Electronic Mailbox: DrugSafety.GPV.US@bayer.com
Facsimile: (973) 709-2185
Address: Global Pharmacovigilance - USA
Mail only: Bayer HealthCare
P.O. Box 915
Whippany, NJ 07981-0915
Address: 100 Bayer Blvd., Whippany, NJ 07981

Reports for all Bayer products can also be phoned in via our Clinical Communications Dept.: 1-888-842-2937

7.6.3 Reporting to BMS

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety.
- In addition to the definition of SAEs above, BMS also includes the following a SAE: Potential drug induced liver injury (DILI) is also considered an important medical event; Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE; Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.
- If the BMS safety address is not included in the protocol document (e.g. multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.
- The BMS SAE form should be used to report SAEs. If the BMS form cannot be used, another acceptable form (i.e. CIOMS or Medwatch) must be reviewed and approved by BMS. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).
    - Other important findings which may be reported by the as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data

monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

For studies conducted under an Investigator IND in the US include the following:
For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.
MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.

- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
    - If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

7.6.4 SAE Reporting to Incyte

Initial reports

The Investigator reports to Incyte every SAE, regardless of suspected causality, which occurs after the subject has signed informed consent and up to the time that subject has completed the trial, including any post-treatment follow-up required by the protocol. Such cases are regarded as originating in the IST for the purpose of notification to Incyte.

The investigational site notifies Incyte of an SAE within 24 hours of the Investigator becoming aware of the SAE, regardless of causality to the investigational product.

The investigational site records all SAE details on the Serious Adverse Event Report Form, or on the SAE form being used by the Investigator conducting the trial, and e-mails the report to Incyte via the address: IncytePhVOpsIST@incyte.com.

If necessary, the Incyte PhV representative or designee queries the investigational site (within 48 hours of receipt) for additional information to ensure a valid case prior to distributing the report for internal Incyte review.

The Incyte PhV representative, in conjunction with the Incyte review team, ensures that all information available at the time, which is relevant to the medical/safety evaluation of the report, is collected and included without compromising the timeframes for regulatory reporting.

If only partial information is available, the report will not be delayed and must be reported to satisfy the reporting timeframe. Any additional information should be collected for a follow-up report to Health Authorities (HAs).

Follow-up reports

When new information regarding the SAE becomes available, the investigational site personnel update all relevant data on the appropriate SAE Report Form, or equivalent, with any new or changed information and send the follow-up SAE report to Incyte within 24 hours of becoming aware of the new information, via e-mail to IncytePhVOpsIST@incyte.com; ablithe@incyte.com.
This includes any SAE that is upgraded to fatal or life-threatening.

Incyte's PhV Service Provider tracks any critical outstanding follow-up information and questions, and contacts the investigational site via a faxed Data Clarification Form (DCF) to request the information until all outstanding queries are resolved.

Regulatory Reporting

If an event is serious, unexpected, and suspected to be related to the investigational product, the event is considered to be reportable to Health Authorities (HAs) as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

An event is determined to be unexpected if it is not listed in the current Reference Safety Information (e.g., Investigator's Brochure (IB)) or when the specificity or severity of the event is not consistent with the current Reference Safety Information.
Fatal or life-threatening SUSARs must be reported to the required HA(s) within 7 calendar days after the Sponsor's initial receipt of information.

All other SUSARs must be reported to the required HA(s) within 15 calendar days after Sponsor's initial receipt of information.

The Sponsor-Investigator reports all SUSARs to the FDA under the Investigator's IND.
Incyte is responsible for the following:

- Meeting expedited reporting requirements to HAs in their respective territories
- Cross-reporting any SUSAR originating from the IST to the applicable Incyte IND(s)
- Distributing Investigator Notifications to Investigators participating in the applicable Incyte IND(s)

PROCEDURE FOR REPORTING PREGNANCY

Data on fetal outcome 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. Within 30 days of learning of the pregnancy, the investigational site completes the Clinical Trial Pregnancy Form (sections I, II, and question 18 in section III) or equivalent, and e-mails the report to Incyte at IncytePhVOpsIST@incyte.com.

7.6.5 Reporting to Gilead

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (i.e., signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the CRF/eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead DSPH

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the CRF/eCRF completion guideline.
  Electronic Serious Adverse Event (eSAE) Reporting Process
- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically, i.e., the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

  Gilead DSPH: Fax: (866) 660-8967
  1-650-522-5477
  Email: pv@ctiseattleSafety_FC@Gilead.com

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

Pregnancy

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term. A spontaneous abortion is always considered to be an SAE. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report

form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH:
Gilead DSPH contact information is as follows:

- **Gilead DSPH:** Fax: 1-650-522-5477
  Email: Safety_FC@Gilead.com

Reporting Other Special Considerations: Special Situations
SAEs consideredAll other special situation reports must be reported on the special situations report form and forwarded to be related (ie, assessed as possibly, probably or definitely related) to study drug or study procedure by the Gilead DSPH within 24 hours of the investigator shall becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situation report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation. Refer to the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.6.6 SAE Reporting to CTI Biopharma, Inc.

All SAEs, irrespective of causal relationship, must be reported to CTI within 24 hours of becoming aware of the event via either Fax or e-mail. Please use the CTI SAE form (Appendix D).

Fax: (866) 660-8967
Email: pv@ctiseattle.com

Special Considerations:

- SAEs considered to be related (ie, assessed as possibly, probably or definitely related) to study drug or study procedure by the investigator shall be followed until the event resolves, stabilizes or the patient is lost to follow up.

- SAEs assessed as unrelated to study drug or study procedures shall be followed for 30 days after last dose of study treatment, or until the event resolves, returns to baseline, stabilizes or the patient is lost to follow-up, whichever comes first.
- An SAE form should be completed for any event for which doubt exists regarding its seriousness. If an ongoing SAE changes in intensity, relationship to study drug, or as new information becomes available and/or known for the event, a follow-up SAE Report form should be completed and sent to the CTI within 24 hours of the change in SAE assessment.
- Any SAE that occurs after study completion and is considered by the investigator to be related to pacritinib should be reported to CTI.

A narrative outlining the details of the SAE and treatment and outcome are to be included on the SAE form. The narrative must state whether there is a reasonable possibility that study drug caused the event. Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event, should be submitted as soon as the information becomes available.

8. PHARMACEUTICAL AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 Agent Accountability

The Investigator, or a responsible party designated by the Investigator at each site, must maintain a careful record of the inventory and disposition of the study agent. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).
http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm
Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities.

The Investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study medication until the end of the study. The Investigator or designee must maintain records that document:

- investigational product delivery to the study site
- the inventory at the site
- use by each subject including pill/unit counts from each supply dispensed
- return to the Investigator or designee

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study subjects.
The investigational product must be used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the subjects were provided the correct study medication specified.

Completed accountability records will be archived by the site. At the completion of the study, the Investigator or designee will oversee shipment of any remaining study drug back to the

manufacturer for destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, prior written approval must be obtained from the manufacturer or manufacturer's study drug distributor.

Please refer to the Pharmacy Manual located in the separate Study Operations Manual for details on drug supply, ordering, and shipment process.

8.2 Study Agent(s)

Study Agents	Anticipated Start dose if no modifications
Sorafenib	400 mg po bid
Sunitinib	50 mg po QD
Dasatinib	140 mg po QD
Ponatinib	45mg po QD
Ruxolitinib	Initial doses of 5, 10, 15 or 20 mg po BID will be administered based on platelet counts at the start of the study (C1D1)
Idelalisib	150 mg po BID
Pacritinib	200 mg po BID

8.2.1 Sorafenib

Product description: Sorafenib (Nexavar®), a multikinase inhibitor targeting several serine/threonine and receptor tyrosine kinases, is the tosylate salt of sorafenib. Each, red, round film-coated tablet contains sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib and the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide and ferric oxide red.

Product Identification: Sorafenib is provided in one strength: Oral Tablet, 200mg.

Packaging and Labeling of sorafenib: Sorafenib tablets are supplied as round, biconvex, red film-coated tables, debossed with the "Bayer cross" on the side and "200" on the other side, each containing sorafenib tosylate equivalent to 200 mg of sorafenib. Bottles contain 120 tablets.

Storage andHandling of sorafenib: Store at 25° C (77°F); excursions permitted to 15-30° C (59-86°F). Store in a dry place.

Dispensing: It is the responsibility of the investigator to ensure that sorafenib is only dispensed to study subjects. Sorafenib must be dispensed only from official study sites by authorized personnel according to local regulations. The investigator (or assigned designee, i.e. study pharmacist) will dispense the proper number of tablets to the subject to satisfy dosing requirements for the study. The containers provided to the subject should be labeled with proper instructions for use. The lot numbers, dosing start dates and the number of tablets must be recorded on the drug accountability pages of record for the site. The subject must be instructed to return all unused sorafenib in the provided packaging at each subsequent visit.

Dosage of sorafenib: The recommended daily dose of sorafenib is 400 mg (2 x 200 mg tablets) taken twice daily, without food (at least 1 hour before or 2 hours after eating). If the morning or

the evening dose is delayed for more than 4 hours, the subject should skip this dose and resume dosing with the next dose per the original schedule in order to prevent overdosing. Treatment will begin on Day 1 of the study and continue daily until disease progression or until an unacceptable toxicity occurs which would require delay, modification or discontinuation of study therapy.

8.2.2 Sunitinib

Product Description: Sunitinib malate (SUTENT®) is a yellow to orange powder with a pKa of 8.95. The solubility of sunitinib malate in aqueous media over the range pH 1.2 to pH6.8 is in excess of 25 mg/mL. Capsules are supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5 mg, 25 mg or 50 mg of sunitinib together with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients.

Product Identification: Sunitinib is provided in three different strengths including a 12.5 mg capsule, 25mg and a 50 mg capsule. Both are hard gelatin capsules with orange cap and orange body, printed with white Pfizer and 12.5 or 25 or 50mg respectively.

Packaging: Sunitinib is packaged in bottles of 28

Storage, Handling and Dispensing of Sunitinib: Sunitinib should be stored at 25°C (77° F). Excursions permitted to 15-30°C (59-86°F). Store in the original container, protect from light and moisture. Dispensing is to be that consistent with ward properties for oral chemotherapy treatments.

Dispensing: Subjects will take the sunitinib once daily by mouth with or without food.

Dosage of Sunitinib: The starting dose of sunitinib is one 50mg oral dose, taken once daily.

8.2.3 Dasatinib

Product Description: Dasatinib tablets are white to off-white, biconvex, film-coated tablets containing dasatinib, with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

Product Identification: Dasatinib is provided in number of different strengths:

- **20 mg:** Each white-to-off-white, biconvex, round, film-coated tablet with "BMS" debossed on one side and "527" on the other side, contains dasatinib 20 mg.
- **50 mg:** Each white-to-off-white, biconvex, oval, film-coated tablet with "BMS" debossed on one side and "528" on the other side, contains dasatinib 50 mg.
- **70 mg:** Each white-to-off-white, biconvex, round, film-coated tablet with "BMS" debossed on one side and "524" on the other side, contains dasatinib 70 mg.
- **80 mg:** Each white-to-off-white, biconvex, triangular, film-coated tablet with "BMS" and "80" (BMS over 80) debossed on one side and "855" on the other side contains dasatinib 80 mg.
- **100 mg:** Each white-to-off-white, biconvex, oval, film-coated tablet with "BMS 100" debossed on one side and "852" on the other side, contains dasatinib 100 mg.

- **140 mg:** Each white-to-off-white, biconvex, round, film-coated tablet with "BMS" and "140" (BMS over 140) debossed on one side and "857" on the other side contains dasatinib 140 mg.

Each bottle is labeled in an open label manner. Labels contain, at a minimum, the following information: product name, tablet strength, batch number, directions for use, storage conditions, and appropriate caution statements.

Storage, Handling and Dispensing of Dasatinib: Bottles containing dasatinib tablets should be stored at 15-25°C. The investigation product should be stored in a secure area according to local regulations. The investigator is responsible for ensuring that it is dispensed only to study subjects and only from official study sites by authorized personnel, as dictated by local regulations. The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity). If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact BMS immediately. Handling and disposal of the dasatinib will be per OHSU guidelines for oral antineoplastic agents and unused tablets in the provided packaging will be returned to study staff.

Dosage of Dasatinib: Dosages are routinely 100mg a day (either as 100mg daily or 50mg bid) or 140mg daily. Although the 100 mg dose had been found to be better tolerated, is effective in CML, and has been the dose safely combined with cytotoxic chemotherapy, given the potential for rapid progression, target protein turnover, poorly defined dose-specific PD/PK in AML, the 140 mg dose has been chosen for this study. If a dose is missed this should be documented and the missed dose is not to be replaced. However if vomiting occurs within 30 minutes of intake, that dose may be repeated. Dasatinib may be taken without regard to food; the tablets should not be broken, crushed, or chewed. Thus, the tablet should be swallowed whole. Antacid therapy should be avoided 2 hours before and two hours after dasatinib ingestion. Dose interruptions and adjustments will be made for drug toxicity.

8.2.4 Ponatinib

Product Description: Ponatinib (Iclusig®) is a kinase inhibitor indicated for the treatment of CML (chronic, accelerated and blast phase), ALL with BCR-ABL positivity. It is an off-white to yellow powder. The solubility decreases with increasing pH. Ponatinib tablets are available as white, round, film coated tablets for oral administration. Each tablet contains ponatinib hydrochloride equivalent to 15 or 45mg ponatinib with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate and a tablet coating. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol and titanium dioxide.

Product Identification: Ponatinib is a round, white, film-coated tablets with debossed “A5” on one side and plain on the other side.

Packaging and Labeling of Ponatinib: Ponatinib tablets are supplied in tamper resistant bottles with 30-180 tablets in each bottle.

Storage, Handling and Dispensing of Ponatinib: Ponatinib tablets, either 15mg or 45mg, should be stored at 25° C (77°F); excursions between 15°-30°C (59°-86°F). The Investigator (or

assigned designee, i.e., study pharmacist) will dispense the proper number of capsules to the subject to satisfy dosing requirements for the study. The containers provided to the subject should be labeled with proper instructions for use. The lot numbers, dosing start dates and the number of capsules for each dosage strength must be recorded on the drug accountability pages of record for the site.

Dosage of Ponatinib: The recommended dose of ponatinib is 45 mg every 24 hours. The tablets need to be taken whole and should not be crushed or dissolved. Patients will take the prescribed number of tablets with water, with or without food, at approximately the same time each day. Subjects should not consume grapefruit products and other foods that are known to inhibit CYP3A4 at all times during ponatinib treatment. If a dose is missed either due to patient, pharmacy, or provider error, this must be documented. Patients who forget to take their dose more than 6 hours after it is due should not make up the missed dose. Patients who vomit after taking their dose should not make up that dose, but take the next dose at the planned time, if clinically indicated.

8.2.5 Pacritinib

Product Description: Pacritinib is an oral tyrosine kinase inhibitor (TKI) with activity against two important activating mutations: Janus Associated Kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3). For use in clinical studies as an oral agent, pacritinib is supplied as size #0 hard gelatin capsules with gray bodies and red caps. Capsules contain 100 mg pacritinib (free base) and the following inactive ingredients: microcrystalline cellulose NF, polyethylene glycol 8000 NF, and magnesium stearate NF. The capsule gelatin is bovine derived.

Product Identification: Pharmacies at investigational sites will receive subject-specific vials containing 120 capsules of pacritinib packaged in 200 mL high-density polyethylene bottles with child-resistant closures.

Storage, Handling and Dispensing of Pacritinib: Drug product should be stored in the pharmacy, hospital, clinic, or warehouse at controlled room temperature, 20°C to 25°C (68°F to 77°F), with excursions allowed between 15°C to 30°C (59°F to 86°F). Patients should be instructed that storage temperatures for pacritinib in the home should be below 30°C (86°F).

Dosage of Pacritinib: The recommended dose of pacritinib is - 200 mg BID.. The tablets need to be taken whole and should not be crushed or dissolved. Patients will take the prescribed number of tablets with water, with or without food, at approximately the same time each day. Subjects should not consume grapefruit products and other foods that are known to inhibit CYP3A4 at all times during -pacritinib treatment. If a dose is missed either due to patient, pharmacy, or provider error, this must be documented. Patients who forget to take their dose more than 6 hours after it is due should not make up the missed dose. Patients who vomit after taking their dose should not make up that dose, but take the next dose at the planned time, if clinically indicated.

8.2.6 Ruxolitinib

Availability: Ruxolitinib will be provided by Incyte Corporation and shipped directly to each site by Incyte or its distributor. Each site will be responsible for contacting Incyte or its

distributor for study drug supply.

Route of administration: Doses should be taken by mouth in the morning and evening, approximately 12 hours apart, and without regards to food.

Study Drug Packaging, Labeling and Preparation: Ruxolitinib Phosphate tablets will be provided as 5 mg tablets packaged as 60 count in high-density polyethylene bottles. All bottles of Incyte investigational product contain the following language: "Caution: New Drug—Limited by Federal law to investigational use."
IIncyte will be responsible for quality and stability of the drug for shipment to sites. Incyte will also communicate any information related to manufacturing issues and expiration dates for each site's shipment.

Study Drug Storage and Stability: The bottles of tablets should be stored at room temperature, 15°C to 30°C (59°F to 86°F). Stability studies will be conducted on clinical batches to support the clinical trial.

8.2.7 Idelalisib

Availability: Idelalisib will be provided by Gilead Science and shipped directly to each site by Gilead or its distributor. Each site will be responsible for contacting Gilead or its distributor for study drug supply.

Route of administration: Doses should be taken by mouth in the morning and evening, approximately 12 hours apart, and without regards to food.

Study Drug Packaging, Labeling and Preparation: Idelalisib will be provided in tablets intended for oral administration. Each tablet contains either 100 mg or 150 mg of idelalisib with the following inactive ingredients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate and a tablet coating. The tablet coating consists of polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide and of FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake (for the 100 mg tablet) and red iron oxide (for the 150 mg tablet).
150 mg tablets: pink, oval-shaped, film-coated tablet debossed with "GSI" on one side and "150" on the other side.
100 mg tablets: orange, oval-shaped, film-coated tablet debossed with "GSI" on one side and "100" on the other side.. Idelalisib tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 60 tablets and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner. Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Refer to Section 2.4.

10. STUDY PROCEDURES AND SCHEDULE OF EVENTS

10.1 Screening/Baseline Visit

Screening assessments will be performed at standard of care visits scheduled for known or suspected relapsed/refractory acute leukemia. The patient will be offered a Screening Consent to determine trial eligibility. Once consent is obtained, a peripheral blood and bone marrow biopsy sample taken at this or a subsequent SOC visit will be used for drug sensitivity testing and for baseline peripheral blood and marrow blast counts. If the patient is found to be eligible to receive study treatment, treatment must begin within 14 days after obtaining the baseline marrow and peripheral blood samples. At OHSU, the results from IRB 4422 (PI Loriaux) may be used to determine sensitivity/eligibility if the sample was obtained within 14 days of starting treatment using the IDE approved inhibitor assay. Baseline samples are required to assess treatment efficacy, and these samples should be taken as close to the initiation of treatment as possible. If treatment has not begun within 14 days, new baseline marrow and peripheral blood samples must be obtained before treatment can begin. Patients that are eligible for treatment will sign a second consent approving treatment with study drug and undergo any additional screening required for treatment.

Investigators at participating sites will identify potential subjects, send baseline samples by overnight delivery, and send source documents that support eligibility to OHSU within 10 days and in accordance with study protocol. The OHSU coordinating center team will verify eligibility, completeness of documents, enter registration information into the Knight CRMS, and assign a study number/identifier. The coordinating center will send an email including a formal inhibitor screening report with eligibility/treatment assignment to the participating site, verify registration, and assign a participant number/identifier. Study treatment cannot begin until OHSU has provided documentation of the registration and eligibility to the subsite.
A detailed description of protocol required procedures and assessments is provided in the Schedule of Events (Section 10.7). Refer to the Study Operations Manual for specific enrollment instructions.

For non OHSU sites, samples will be shipped to OHSU per the separate sample manual instructions.

10.2 Study Treatment

For the majority of kinase inhibitors used, each 4 week (28 day) period that a subject is on study will be considered a study cycle. Additional testing or assessment should be performed as medically indicated.

Study visits will include the following assessments: (+/-3 days)

- Physical examination will occur every 2 weeks (14 days ± 3 days) for every cycle the subject is on study.
- ECOG performance status at each PE
- Vital signs (weight, blood pressure, pulse, body temperature) at each PE
- ECG (12- Lead) during screening (≤ 14 days before treatment) and as clinically indicated per provider discretion.
- Bone marrow aspirate and biopsy on days 14 and 28 (±3 days) of cycle 1 and then as

clinically indicated. The inhibitor assay will be performed on all marrow samples with adequate cell numbers to monitor drug sensitivity.

- Hematology (CBC with 5 part differential, hemoglobin and platelets) collected on day 1,7, 14, 21, 28 of Cycle 1, then day 14 and 28 each additional cycle (±3 day window)
- Serum chemistries collected on days 1 and 14 of each cycle (±3 day window) (sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, total bilirubin, ALT, AST, total protein, alkaline phosphatase, albumin, uric acid, calcium lactic dehydrogenase [LDH], phosphate, magnesium) Concomitant medication
- Adverse event assessment. Toxicities and adverse experiences will be assessed at each visit using the NCI Common Toxicity Criteria for Adverse Events v4.0 (CTCAE, see appendix B).

Pharmacokinetic Research Sample Collection:

Peripheral blood samples will be collected (between 2-5 cc green top) at the following time points. Samples will be banked for future studies. Samples will be shipped to OHSU per instructions in the separate sample manual.

- Pre-PK sample collected at screening or Cycle 1, day 1 prior to study drug administration
- Cycle 1 day 7, 14 and 21 pharmacokinetic at predose and 4 hours post dose, then pre dose on day 1 of each subsequent cycle
- At progression, single pharmacokinetic collected

10.3Discontinuation/Replacement of Study Therapy

Subjects who demonstrate progression will be immediately taken off of their assigned study drug. Although the primary endpoint for the study is a ≥25% decrease in bone marrow blast count at any evaluable time point within the 28 day treatment window, patients who do not meet the primary outcome are eligible to stay on drug if they have stable disease and are tolerating treatment. Once a patient is discontinued from treatment at the discretion of the investigator, and if the subject so chooses, the subject may be considered for an alternative secondary study drug based on re-testing in the ex-vivo inhibitor/kinase target identification process. However, prior to study enrollment, the subject will need to meet all eligibility criteria and re-consent for the trial. Subject will re-start Cycle 1 and level of tumor measurement at that time will become the new baseline.

OHSU Coordinating Center should be notified within one working day of any patient that is taken off study.

10.4 Subject Discontinuation

Study drug must be immediately discontinued for the following reasons:

- Disease progression
- Voluntary subject withdrawal of consent
- Investigator's decision that is in the subject's best interest to withdrawal
- If the subject becomes pregnant
- Noncompliance
- Significant protocol violation
- For any reason, at the Investigator's discretion

10.5 Early Study Termination by the Coordinating Center

Reasonse for early study termination include:

- Unsatisfactory Enrollment
- Toxicity
- Incomplete or inaccurate data recording
- Lack of adherence to the protocol or applicable regulatory guidelines in the conduct of the study

If a subject withdraws consent for any further participation in the study, he or she should be contacted to obtain information about the reason(s) for discontinuation and collection of any potential adverse events. For all other reasons for discontinuation from the study treatment phase, the subject should return to the clinic for the end of treatment visit within 5 days of discontinuing study drug. If a subject has disease progression during a study visit, this visit can qualify as the end of treatment visit and long-term follow-up clinical assessments.

10.6 Follow-up Visits

Refer to Section 10.2 for a detailed description of study procedures. Follow-up is independent of response status.

10.7 Schedule of Events

	Screening	Cycle 1* (C1D28 = C2D1)					Cycle 2 and beyond			End of Treatment	Follow-up per SOC
		Day 1	Day 7	Day 14	Day 21	Day 28	Day 1	Day 14	Day 28		
Visit Window	≤ 14 days before treatment		±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days		
Informed consent	X										
Inclusion/ Exclusion Review	X										
Medical History and Demographics	X										
Disease and Previous anti-neo-plastic history	X										
Physical Examination	X	X		X			X	X		X	X
Vital signs, including blood pressure	X	X		X			X	X		X	X
ECOG Performance Status	X	X		X			X	X		X	X
CBC with diff; including # of atypical/blasts seen	X	X	X	X	X	X[1]		X[2]	X[1,2]	X	X
Serum Chemistries[3]	X	X		X			X	X		X	X
Serum Lipase & Amylase (ponatinib only after screening) (lipase for sorafenib only after screening)	X	X		X			X	X			
Lipid Panel	X										
INR/PTT	X										
Pregnancy test[4]	X										
Urinalysis (dipstick and Micro)[5]	X										
ECG (12 lead)[6]	X	As clinically indicated per investigator discretion									
CXR (dasatinib only) (PA/LAT)[7]	X	As clinically indicated per investigator discretion									
Bone marrow biopsy cytogenetics and FISH[8]	X			X		X			X[2,8]		
Baseline bone marrow and peripheral blood for ex-vivo inhibitor kinase target identification, correlative studies, SOC cytogenetics, SOC FISH, skin biopsy one time during study	X			X		X		X	X		
Pharmacokinetic peripheral blood	X[9]	X[9]	X[10]	X[10]	X[10]		X[11]		X[12]		
Adverse Events (30 days post last dose study drug)		Continuous							X	X	
Concomitant medications		Continuous							X	X	
Disease status and Survival		X							X	X	

*In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 28 days; however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 6. If the interval is increased, all procedures except imaging should be performed based on the new dosing schedule.

[1]Performed as part of bone marrow analysis

[2]As clinically indicated

[3]Chemistry includes sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, total bilirubin, ALT, AST, total protein, alkaline phosphatase, albumin, uric acid, calcium. Lactate dehydrogenase (LDH), phosphorus, magnesium

[4]Pregnancy (if applicable) must be performed within 72 hours of starting study drug.

[5]Per package insert for sunitinib, perform baseline and periodic urinalyses during treatment, with followup measurement of 24-hour urine protein as clinically indicated.
[6]And as clinically indicated with any dose adjustments for cardiac toxicity
[7]Chest x-ray obtained at baseline for dasatinib and then as clinically indicated per investigator discretion
[8]FISH will be conducted per institutional guidelines; Day 28 marrow for cycle 2 and beyond is per provider discretion based on the disease status of the patient.
[9]Screening OR Day 1 (pre-dose) PK sample may be used as a baseline sample. If taken on C1D1, it must be prior to administration of study drug.
[10]Pre-dose and 4 hours post dose
[11]Pre-dose only
[12]At relapse

11 MEASUREMENT OF EFFECT

For the purposes of this study, patients will be evaluated for response by SOC and weekly peripheral blood blast counts and by marrow blast counts at days 14 and 28 of cycle one. After cycle 1, bone marrow assessments will be performed as clinically indicated.

11.1 Definition of Response for the Primary Endpoint

The primary objective, defined as a ≥ 25% decrease in bone marrow blast count from baseline, and overall response rates (PR plus CR) will be determined for each study subject throughout the study period.

11.2 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment through the end of cycle 1 or until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Bone marrow blast counts will be followed at pre-determined intervals and used to monitor response.

Partial responses and complete responses will be determined (secondary objectives) using formal AML and ALL response criteria defined in Section 11.3 and 11.4.

11.3 Response criteria for AML

Response Criterion	Time of Assessment	Neutrophils (µL)	Platelets (µL)	Bone Marrow Blasts (%)	Other
Early treatment assessment	7-10 days after therapy	NA	NA	<5	
Morphologic leukemia-free state	Varies by protocol	NA	NA	<5	Flow cytometry EMD
Morphologic CR	Varies by protocol	>1000	>100,000	<5	Transfusion EMD
Cytogenetic CR	Varies by protocol	>1000	>100,000	<5	Cytogenics – normal, EMD
Molecular CR	Varies by protocol	>1000	>100,000	<5	Molecular – negative, EMD
Partial remission	Varies by protocol	>1000	>100,000	> 50 or decrease to 5-25	Blasts <5% if Auer rod positive

EMD, extramedullary disease; CR, complete remission
Modified from Cheson et al(30)

AML Complete Remission (CR) is defined as all of the following:

- Peripheral blood counts:
  - ANC ≥ 1,000/mm^3
  - Platelet count ≥ 100,000/mm^3
- Bone marrow:

- No Auer rods
- <5% blast cells in a 200-cell differential

- No extramedullary leukemia

AML Complete remission with incomplete hematopoietic recovery (CRi) is defined as all of the following:

- Satisfying all criteria for CR except for
  - ANC < 1,000/mm^3 and/or
  - Platelet count < 100,000/mm^3,but not requiring platelet transfusion

AML Confirmed complete remission with or without complete hematopoietic recovery is defined as the following:

- Satisfying all criteria for CR or CRi at least 30 days after initial determination of CR

AML Complete remission with persistent morphologic dysplasia (CRd) is defined as the following:

- CR or CRi as defined above but marrow and/or peripheral blood show persistent dysplasia, as determined by hematopathology review. Local slides may be requested to be sent to coordinating site for additional review as per Coordinating Center PI request

AML Cytogenetic complete remission (CRc) is defined as the following:

- CR or CRi as defined above with disappearance of previous (pre-study) cytogenetic abnormalities, i.e., return to normal karyotype

Partial remission (PR) is defined as all of the following:

- Peripheral blood counts:
  - ANC ≥ 1,000/mm3 (≥ 1.0 x 109/L);
  - Platelet count ≥ 100,000/mm3 (≥ 100.0 x 109/L).
- Bone marrow:
  - Decrease in the pre-treatment blast percentage by at least 50%, and reduction to a value between 5% and 25% of the nucleated cell differential count
  - If Auer rods are present, reduction in blast percentage to < 5%.
- No extramedullary leukemia.

Progression is defined as a ≥ 50% increase in leukemic bone marrow blasts.

11.4 Response Criteria for ALL

ALL Complete Response (CR)

- **Complete Hematologic Response (CHR)** is defined as the following:
  - Bone marrow cellularity greater than 20% with maturation of all cell lines and less than 5% blasts
  - Recovery of granulocyte count to greater than 1,500mm^3 and platelet count greater than 100,000mm^3, and no leukemic blasts in the peripheral blood
  - Resolution of any detectable extramedullary leukemia. Isolated and stable splenomegaly is not considered extramedullary disease
- **Complete Cytogenetic Response (CCyR)** is defined as:

- Absence of previously detected abnormalities in bone marrow by conventional cytogenetic metaphases or FISH
- **Progression** is defined as a ≥ 50% increase in leukemic bone marrow blasts

ALL Minimal Residual Disease (MRD)
- **For Bone Marrow Involvement only**
  - Detection of residual blast cells by flow, with a sensitivity of 10^{-2} **AND**
  - For Ph+ ALL, RT-PCR for BCR/ABL with a sensitivity of 10^{-3}

ALL Partial Response (PR)
- **For Bone Marrow Involvement**
  - Reduction of ≥50% of blasts

ALL Progression is defined as a ≥ 50% increase in leukemic bone marrow blasts

11.5 Duration of Overall Response and Stable Disease

11.5.1 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

11.5.2 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.6 Progression-Free Survival

Time from the start of study drug treatment to death, regardless of cause of death, or date of disease progression defined as a ≥ 50% increase in leukemic bone marrow blasts, whichever occurs first.

11.7 Overall Survival (OS)

Time from the date of subject registration to death, regardless of causes of death. Those who are alive at the end of the study are censored at the date of last contact.

11.8 Response Review

At the completion of the study, assessment of response e.g. changes in blasts counts (peripheral or bone marrow) will be reviewed by an independent OHSU hematopathologist and assessed by an independent clinician.

12 DATA REPORTING/REGULATORY REQUIREMENTS

12.1 Data Collection and Storage

Information for each participant will be collected and entered directly into an existing electronic

relational database. Each site will be responsible for entry of data for patients accrued at that site with all correlative data entered by personnel at OHSU, as detailed below.

iMedidata Rave, the database that will be used for this trial, was built to house voluminous, diverse data sets in a three-dimensional, relational setting whereby all information for a given patient can be viewed and correlated with all other pieces of information. This database was launched in October 2011. It is a web-based interface that references data, which is stored on a secure server such that all information collected for any patient can be traced through a hierarchy to show the exact lineage of that information stream. In addition, a sophisticated query/report function allows for complex analyses of data that has been collected and can thus facilitate integration of diverse data types. This database is supported by a web-portal login, and team members currently teams at all trial sites will have login credentials and have been trained in procedures for entering, accessing and storing data. This will facilitate information being stored in a unified format and location, which will be important for the long-distance collaborations of this trial.

This database utilizes a tiered user format whereby each user is defined based on access to read/edit each field as well as privileges of viewing protected health information (PHI). Since every data field is strictly defined as to whether PHI is present in that field, users lacking PHI privileges will be completely shielded from viewing such information. In addition, all information is stored on an encrypted server and access to the database is password protected. Finally, this database undergoes a rigorous back-up and audit trail such that information is never in danger of being permanently lost. Hence, the security and integrity of this database far surpasses requirements for data storage.
Clinical and demographic information about each patient (i.e. gender, race, ethnicity, date of birth, white blood cell count, extended differentials, karyotype/cytogenetics, etc.) will be entered directly into this database by each site at which a new patient is enrolled onto the trial. Data from correlative studies will be entered by laboratory personnel at OHSU.

Quality assurance will be conducted as outlined in section 12.7 under data safety and monitoring. Per OHSU guidelines (refer to Appendix D– "Human Research Protection Program – Investigator Guidance for Protocol Deviations"), moderate and major protocol deviations will be captured in iMedidata Rave®. Minor administrative deviations that are not otherwise documented in the system will also be captured in the regulatory study binder and if patient-specific in iMedidata Rave®. Minor protocol deviations that are procedure related (study procedure not performed/results not available) will be captured in the study database by study staff by recording that a procedure was not done. An example of a minor protocol deviation is a blood draw that did not occur. Note - If modification of the study medication dose was made without the required test results being available, then a protocol deviation would be recorded on the Protocol Deviation log and reported. At the end of a study, minor protocol deviations will be summarized.

12.2 Multicenter Guidelines

This protocol will adhere to the guidelines of the OHSU Knight Multi-Center Investigator Initiated Trials Coordinating Center Operations Manual.

OHSU Coordinating Center will manage trial data in the following ways:

- Confirm that all sites have received and are using the most recent version of the protocol.

The protocol must not be rewritten modified by anyone other than the OHSU Knight Principal Investigator. Documentation of the version that was sent to the site must be kept in the regulatory binders.

- Confirm that the protocol and informed consent form have local IRB approval at each site prior to registration of the first subject. Documentation of IRB approval from other sites for continuing review must be submitted and kept in the binder.
- Provide centralized subject registration in the clinical research management system
- Ensure collection and review of applicable source documents and case report by the OHSU PI to ensure protocol compliance
- Maintain documentation for all SAE reports and submit a summary of all AE, SAE and unanticipated problems (UP) to the Knight DSMP
- Prepare quarterly summary reports of SAEs and UPs from all sites
- Ensure that relevant IRB correspondence and study status changes are communicated to all participating sites within five business days. Any changes that affect patient safety of study enrollments will be communicated immediately
- Submit documentation to the FDA such as protocol amendments, annual reports, SAE reports for unexpected, fatal or life-threatening events that are associated with the use of the study drug

Participating sites must submit regulatory documents including, but not limited to the following:

- Current CV (signed and dated) for each investigator
- Current medical license number for physician investigators
- Current signed FDA Form 1572
- Certificate of completion of institution-required human subject training course, the NIH online training in the protection of human research subjects or other appropriate training
- Documentation of institutional Conflict of Interest
- IRB approved site-specific ICF (must be reviewed and approved by OHSU PI and study team prior to submission to the local IRB
- All IRB approved documents and approval memos
- Delegation log
- Data Safety and Monitoring Plan (DSMP)
- iMedidata data entry completed within 21 business days of study visit

12.3 Protocol Review

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute Clinical Research Review Committee (CRRC) and the appropriate Institutional Review Board (IRB) prior to any subject being consented on this study. All sites must have IRB approval of protocol by the IRB of record before consenting any subjects.

12.4 Informed Consent

Written informed consent will be obtained from all subjects, or the legally authorized representative of the subject, participating in this trial, as stated in the Informed Consent section of the case of Federal Regulations, Title 21, Part 50. If a subject's signature cannot be obtained, and for all subjects under the age of 18, the investigator must ensure that the informed consent is signed by the subject's legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the subject's medical record.

All study sites must have IRB approval of ICF by the IRB of records before consenting any subjects.

12.5 Changes to Protocol

Any modification of this protocol must be documented in the form of a protocol revision or amendment approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the subject. In that event, the investigator must notify the CRRC and IRB in writing within 10 working days after the implementation. Investigators holding the IDE must notify FDA of substantive changes to the protocol.

Participating study site must submit proposed changes to protocol to the OHSU Coordinating Center for review and endorsement before participating site may implement changes.

12.6 Maintenance of Records

If the investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution, another investigator, or the OHSU Knight Cancer Institute Clinical Trials Office. Records must be maintained according to sponsor or FDA requirements.

12.7 OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.8 OHSU Knight Cancer Institute Data and Safety Monitoring Plan

In addition to complete study and pharmacy files, complete records must be maintained on each subject treated on this protocol. OHSU Knight Cancer Institute, through the auditing function of the Knight Clinical Trials Office, is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, FDA regulations and NIH policies and in accordance with the Data and Safety Monitoring Plan policies and procedures (http://ohsucancer.com/crm).

Locally initiated studies will be audited by OHSU Knight CI Auditor. Newly approved studies may be audited any time after enrollment has been initiated. Each OHSU Knight approved treatment protocol will be audited on an annual basis in accordance with the Knight Data and Safety Monitoring Plan.

Participating Sites

It is the responsibility of each participating site's principal investigator to ensure that the study is conducted in compliance with local IRB standards, FDA regulations, and NIH policies. It is also the responsibility of each site's principal investigator to ensure that quality assurance audits at their site are conducted according to their institution's policies and procedures. The quality assurance audit process provides assurance that reported data accurately reflects the data in the primary subject record.

12.9 Inclusion of Women, Minorities and Children

12.9.1 Inclusion of Women and Minorities

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No subject will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied. The projected gender, racial, and ethnic composition of the study will represent that of the state of Oregon.

Table 1: Population Demographics - Oregon (%)

Ethnic Category	**Sex/Gender**		
	Females	Males	Total
Hispanic or Latino			11.7
Not Hispanic or Latino			88.3
Ethnic Category: Total of all subjects*			100*
Racial Category			
American Indian or Alaskan Native			1.4
Asian			3.7
Black or African American			1.8
Native Hawaiian or other Pacific Islander			0.3
White			83.6
More than one race			3.8
Unknown/Other			5.3
Racial Category: Total of all subjects*			100*
TOTALS	50.4	49.6	100*

Source: U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding.

Table 2: Projected Accrual for the Present Study

Ethnic Category	**Sex/Gender**			
	Females	Males	Unknown	Total
Hispanic or Latino	1	1	0-1	2
Not Hispanic or Latino	24	24	0-1	22
Unknown	0-1	0-1	0-1	0-1
Ethnic Category: Total of all subjects*	25	25	0-1	50 *
Racial Category				
American Indian or Alaskan Native	0-1	0-1	0-1	0-1
Asian	0-1	0-1	0-1	0-1
Black or African American	0-1	0-1	0-1	0-1
Native Hawaiian or other Pacific Islander	0-1	0-1	0-1	0-1
White	23	23	0-1	0-1
More than one race	0-1	0-1	0-1	0-1
Unknown	0-1	0-1	0-1	0-1
Racial Category: Total of all subjects*	25	25	0-1	50

Source: Adapted from U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding.

12.9.2 Inclusion of Children

In accordance with NIH guidelines on the inclusion of children as participants in research involving human subjects, children under the age of 18 years must be included in all human subjects' research, conducted or supported by the NIH, unless there are clear and compelling reasons not to include them. Therefore, proposals for research involving human subjects must include a description of plans for the inclusion of children.

This protocol does not include children for the following reason: No dosing or adverse event data are currently available on the use of this study agent in this way in subjects <21 years of age, therefore, children are excluded from this study but will be eligible for future pediatric trials with this study agent.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a phase II, proof-of-concept trial to evaluate an individualized therapy strategy based on the results from the unique in-vitro inhibitor screen developed at OHSU. A total of 24 patients (not including screen failures) who meet the eligibility criteria will be enrolled and assigned to an individualized therapy based on the results of the in-vitro inhibitor screen. Because of heterogeneity of patients, this study is designed as a single stage, fixed sample size trial. Specifically, there will be no interim analyses or stopping rules due to toxicity, or lack of efficacy. Adverse events will be monitored by the study team as well as the Knight Cancer Institute Data and Safety Monitoring Committee (DSMC).

13.2 Primary and Secondary Endpoints

The primary endpoint is clinical activity, defined as a ≥ 25% decrease in bone marrow blast counts or a ≥25% decrease in peripheral blood blasts at any evaluable time point within the 28-day treatment window. Blast percentages are not interchangeable between peripheral blood and marrow. Secondary endpoints are: overall objective response rates (complete and partial), progression-free survival and overall survival, and to determine clinical activity (defined as ≥ 25% decrease in bone marrow blast counts or a ≥25% decrease in peripheral blood blasts) in subjects who have failed the initial inhibitor but are then treated with another inhibitor identified on repeat pre-clinical (in-vitro) activity testing.

Exploratory endpoints include identification and characterization of active/aberrant kinase pathways and correlation with treatment response, mutational analysis using next generation sequencing, and characterization of aberrant gene expression in primary leukemia samples.

13.3 Analysis Populations

An intent-to-treat (ITT) analysis set includes patients who meet the screening criteria and are assigned to one of the study drugs regardless of actual dose of the drug received. A safety analysis set includes patients who complete at least one dose of the assigned drug, while the per-protocol analysis set includes patients who complete 28 days of the assigned treatment. The ITT analysis set is used to evaluate the primary and secondary efficacy endpoints, while the safety analysis set is used to evaluate the toxicity and safety endpoints. To better understand the effects of the assay-guided treatment strategy, we will also evaluate the primary and secondary endpoints using the per-protocol analysis set.

13.4 Statistical Analysis Plan

Patient demographic and clinical characteristics, including *in vitro* inhibitor cytotoxicity (IC50), will be summarized using descriptive statistics (e.g., proportions for categorical variables, and mean/standard deviation for continuous variables). For the primary endpoint, we will estimate the proportion of patients with clinical activity (≥ 25% decrease in blast percentage within the 28-day treatment window). We will consider the approach worthy of further consideration if we observe at least 4 patients with clinical activity among 24 patients, or equivalently the proportion of patients with clinical activity is significantly greater than 5% (historical rate) at a one-sided 5% significance level. Patients who fail to have a blast count measured within the 28 day treatment cycle will be considered as non-responders (no clinical activity) in the ITT analysis. For the secondary binary endpoints (e.g., target response, clinical activity in subjects who have failed the initial inhibitor but are then treated with another inhibitor identified on repeat pre-clinical (in-vitro) activity testing, objective response), we will present the proportion of patients achieving the endpoint along with its 95% exact binomial confidence interval. For time-to-event endpoints (e.g., OS, PFS), Kaplan-Meier method will be used to estimate the survival curve. Adverse events will be tabulated and summarized according to the NCI CTCAE v. 4.0 as well as key reporting criteria (i.e., grade or seriousness, unanticipated, treatment attribution). For correlative/exploratory studies, we will use either t-test (normally distributed variables) or Wilcoxon rank sum test (non-normally distributed variables) to determine whether the mean of continuous biomarkers or patient factors (e.g., IC50 inhibitor cytotoxicity and kinase target/pathway inhibition level) are significantly different between responding or non-responding patients.

13.5 Sample Size and Power

The sample size is derived under the following null (H_0) and alternative (H_1) hypotheses:

$H_0: p = .05$ versus $H_1: p > .05$

The parameter p represents the proportion of patients who achieve the primary endpoint, i.e. ≥ 25% decrease in bone marrow blast counts at any evaluable time point within the 28 day treatment window. Based on one-sided, exact binomial distribution, the sample size of 24 patients will provide 81% power at $p = .22$ (desired response) with 3% significance level (5% target level). If there are 4 or more responses, we conclude that the response rate is significantly better than the historical rate (5%), and the approach worthy of further investigation. The sample size calculation is performed using PASS 2008 [Hintze J (2008), NCSS, LLS. Kaysville, Utah, www.ncss.com] using "Inequality Tests for One Proportion: Exact Binomial Test". We expect that 20% of screened patients will be eligible for the trial, and therefore a total of 120 patients will be screened.

13.6 Handling of Missing Data

We will use all available data and will not impute missing data. Generally, missing data will be coded as missing or unknown and will be included in the intent-to-treat (ITT) analyses. For the primary endpoint, those without a blast count performed within the 28 day treatment cycle will be considered as non-responders (no clinical activity) in the ITT analysis.

REFERENCES

1. Breems DA, Van Putten WL, Huijgens PC, Ossenkoppele GJ, Verhoef GE, Verdonck LF, Vellenga E, De Greef GE, Jacky E, Van der Lelie J, Boogaerts MA, Lowenberg B. Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol. 2005;23(9):1969-78. doi: 10.1200/JCO.2005.06.027. PubMed PMID: 15632409.
2. Giles F, O'Brien S, Cortes J, Verstovsek S, Bueso-Ramos C, Shan J, Pierce S, Garcia-Manero G, Keating M, Kantarjian H. Outcome of patients with acute myelogenous leukemia after second salvage therapy. Cancer. 2005;104(3):547-54. doi: 10.1002/cncr.21187. PubMed PMID: 15973664.
3. Estey EH. Treatment of relapsed and refractory acute myelogenous leukemia. Leukemia. 2000;14(3):476-9. PubMed PMID: 10720145.
4. Craddock C, Tauro S, Moss P, Grimwade D. Biology and management of relapsed acute myeloid leukaemia. Br J Haematol. 2005;129(1):18-34. doi: 10.1111/j.1365-2141.2004.05318.x. PubMed PMID: 15801952.
5. Jackson G, Taylor P, Smith GM, Marcus R, Smith A, Chu P, Littlewood TJ, Duncombe A, Hutchinson M, Mehta AB, Johnson SA, Carey P, MacKie MJ, Ganly PS, Turner GE, Deane M, Schey S, Brookes J, Tollerfield SM, Wilson MP. A multicentre, open, non-comparative phase II study of a combination of fludarabine phosphate, cytarabine and granulocyte colony-stimulating factor in relapsed and refractory acute myeloid leukaemia and de novo refractory anaemia with excess of blasts in transformation. Br J Haematol. 2001;112(1):127-37. PubMed PMID: 11167793.
6. Ho AD, Lipp T, Ehninger G, Illiger HJ, Meyer P, Freund M, Hunstein W. Combination of mitoxantrone and etoposide in refractory acute myelogenous leukemia--an active and well-tolerated regimen. J Clin Oncol. 1988;6(2):213-7. doi: 10.1200/JCO.1988.6.2.213. PubMed PMID: 3422260.
7. Appelbaum FR, Gundacker H, Head DR, Slovak ML, Willman CL, Godwin JE, Anderson JE, Petersdorf SH. Age and acute myeloid leukemia. Blood. 2006;107(9):3481-5. doi: 10.1182/blood-2005-09-3724. PubMed PMID: 16455952; PMCID: PMC1895766.
8. Erba HP. Prognostic factors in elderly patients with AML and the implications for treatment. Hematology Am Soc Hematol Educ Program. 2007:420-8. doi: 10.1182/asheducation-2007.1.420. PubMed PMID: 18024660.
9. Stone RM. The difficult problem of acute myeloid leukemia in the older adult. CA Cancer J Clin. 2002;52(6):363-71. PubMed PMID: 12469764.
10. Wheatley K, Brookes CL, Howman AJ, Goldstone AH, Milligan DW, Prentice AG, Moorman AV, Burnett AK, United Kingdom National Cancer Research Institute Haematological Oncology Clinical Studies G, Acute Myeloid Leukaemia S. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. Br J Haematol. 2009;145(5):598-605. doi: 10.1111/j.1365-2141.2009.07663.x. PubMed PMID: 19344426.
11. Menzin J, Lang K, Earle CC, Kerney D, Mallick R. The outcomes and costs of acute myeloid leukemia among the elderly. Arch Intern Med. 2002;162(14):1597-603. PubMed PMID: 12123403.
12. Rassenti LZ, Huynh L, Toy TL, Chen L, Keating MJ, Gribben JG, Neuberg DS, Flinn IW, Rai KR, Byrd JC, Kay NE, Greaves A, Weiss A, Kipps TJ. ZAP-70 compared with immunoglobulin heavy-chain gene mutation status as a predictor of disease progression in chronic lymphocytic leukemia. The New England journal of medicine. 2004;351(9):893-901.

Epub 2004/08/27. doi: 10.1056/NEJMoa040857. PubMed PMID: 15329427.
13. Cashen AF SG, O'Donnell MR, et al. Preliminary Results of a Multicenter Phase II Trial of 5-Day Decitabine as Front-Line Therapy for Elderly Patients with Acute Myeloid Leukemia (AML). . Blood (ASH Annual Meeting Abstracts). 2008;2008: 112(Abstract 560).
14. Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, Durrant IJ, Luger SM, Marks DI, Franklin IM, McMillan AK, Tallman MS, Rowe JM, Goldstone AH, Medical Research Council of the United Kingdom Adult ALLWP, Eastern Cooperative Oncology G. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood. 2007;109(3):944-50. doi: 10.1182/blood-2006-05-018192. PubMed PMID: 17032921.
15. Nakao M, Yokota S, Iwai T, Kaneko H, Horiike S, Kashima K, Sonoda Y, Fujimoto T, Misawa S. Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia. 1996;10(12):1911-8. PubMed PMID: 8946930.
16. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, Barrientos JC, Zelenetz AD, Kipps TJ, Flinn I, Ghia P, Eradat H, Ervin T, Lamanna N, Coiffier B, Pettitt AR, Ma S, Stilgenbauer S, Cramer P, Aiello M, Johnson DM, Miller LL, Li D, Jahn TM, Dansey RD, Hallek M, O'Brien SM. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. The New England journal of medicine. 2014;370(11):997-1007. doi: 10.1056/NEJMoa1315226. PubMed PMID: 24450857; PMCID: PMC4161365.
17. Brown JR, Byrd JC, Coutre SE, Benson DM, Flinn IW, Wagner-Johnston ND, Spurgeon SE, Kahl BS, Bello C, Webb HK, Johnson DM, Peterman S, Li D, Jahn TM, Lannutti BJ, Ulrich RG, Yu AS, Miller LL, Furman RR. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110delta, for relapsed/refractory chronic lymphocytic leukemia. Blood. 2014;123(22):3390-7. doi: 10.1182/blood-2013-11-535047. PubMed PMID: 24615777; PMCID: PMC4123414.
18. Flinn IW, Kahl BS, Leonard JP, Furman RR, Brown JR, Byrd JC, Wagner-Johnston ND, Coutre SE, Benson DM, Peterman S, Cho Y, Webb HK, Johnson DM, Yu AS, Ulrich RG, Godfrey WR, Miller LL, Spurgeon SE. Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-delta, as therapy for previously treated indolent non-Hodgkin lymphoma. Blood. 2014;123(22):3406-13. doi: 10.1182/blood-2013-11-538546. PubMed PMID: 24615776; PMCID: PMC4260978.
19. Pillinger G, Loughran NV, Piddock RE, Shafat MS, Zaitseva L, Abdul-Aziz A, Lawes MJ, Bowles KM, Rushworth SA. Targeting PI3Kdelta and PI3Kgamma signalling disrupts human AML survival and bone marrow stromal cell mediated protection. Oncotarget. 2016;7(26):39784-95. doi: 10.18632/oncotarget.9289. PubMed PMID: 27174919; PMCID: PMC5129970.
20. Kohrer S, Havranek O, Seyfried F, Hurtz C, Coffey GP, Kim E, Ten Hacken E, Jager U, Vanura K, O'Brien S, Thomas DA, Kantarjian H, Ghosh D, Wang Z, Zhang M, Ma W, Jumaa H, Debatin KM, Muschen M, Meyer LH, Davis RE, Burger JA. Pre-BCR signaling in precursor B-cell acute lymphoblastic leukemia regulates PI3K/AKT, FOXO1 and MYC, and can be targeted by SYK inhibition. Leukemia. 2016;30(6):1246-54. doi: 10.1038/leu.2016.9. PubMed PMID: 26847027; PMCID: PMC5459356.
21. Karaman MW, Herrgard S, Treiber DK, Gallant P, Atteridge CE, Campbell BT, Chan KW, Ciceri P, Davis MI, Edeen PT, Faraoni R, Floyd M, Hunt JP, Lockhart DJ, Milanov ZV, Morrison MJ, Pallares G, Patel HK, Pritchard S, Wodicka LM, Zarrinkar PP. A quantitative analysis of kinase inhibitor selectivity. Nat Biotechnol. 2008;26(1):127-32. doi: 10.1038/nbt1358. PubMed PMID: 18183025.
22. Stone RM, DeAngelo DJ, Klimek V, Galinsky I, Estey E, Nimer SD, Grandin W,

Lebwohl D, Wang Y, Cohen P, Fox EA, Neuberg D, Clark J, Gilliland DG, Griffin JD. Patients with acute myeloid leukemia and an activating mutation in FLT3 respond to a small-molecule FLT3 tyrosine kinase inhibitor, PKC412. Blood. 2005;105(1):54-60. doi: 10.1182/blood-2004-03-0891. PubMed PMID: 15345597.
23. Cortes J, Foran J, Ghirdaladze Dea. AC220, a potent selective second generation FLT3 receptor tyrosine kinase (RTK) inhibitor, in a first-in human (FIH) phase 1 AML study. . American Society of Hematology2009.
24. Fiedler W, Serve H, Dohner H, Schwittay M, Ottmann OG, O'Farrell AM, Bello CL, Allred R, Manning WC, Cherrington JM, Louie SG, Hong W, Brega NM, Massimini G, Scigalla P, Berdel WE, Hossfeld DK. A phase 1 study of SU11248 in the treatment of patients with refractory or resistant acute myeloid leukemia (AML) or not amenable to conventional therapy for the disease. Blood. 2005;105(3):986-93. doi: 10.1182/blood-2004-05-1846. PubMed PMID: 15459012.
25. Verstovsek S, Tefferi A, Cortes J, O'Brien S, Garcia-Manero G, Pardanani A, Akin C, Faderl S, Manshouri T, Thomas D, Kantarjian H. Phase II study of dasatinib in Philadelphia chromosome-negative acute and chronic myeloid diseases, including systemic mastocytosis. Clin Cancer Res. 2008;14(12):3906-15. doi: 10.1158/1078-0432.CCR-08-0366. PubMed PMID: 18559612; PMCID: PMC5018899.
26. Pratz KW, Cho E, Levis MJ, Karp JE, Gore SD, McDevitt M, Stine A, Zhao M, Baker SD, Carducci MA, Wright JJ, Rudek MA, Smith BD. A pharmacodynamic study of sorafenib in patients with relapsed and refractory acute leukemias. Leukemia. 2010;24(8):1437-44. doi: 10.1038/leu.2010.132. PubMed PMID: 20535150; PMCID: PMC2921005.
27. Mesa RA, Vannucchi AM, Mead A, Egyed M, Szoke A, Suvorov A, Jakucs J, Perkins A, Prasad R, Mayer J, Demeter J, Ganly P, Singer JW, Zhou H, Dean JP, Te Boekhorst PA, Nangalia J, Kiladjian JJ, Harrison CN. Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial. Lancet Haematol. 2017;4(5):e225-e36. doi: 10.1016/S2352-3026(17)30027-3. PubMed PMID: 28336242.
28. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Joint ESCAAHAWHFTFftUDoMI, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020-35. doi: 10.1161/CIR.0b013e31826e1058. PubMed PMID: 22923432.
29. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, Hatsukami TS, Higashida RT, Johnston SC, Kidwell CS, Lutsep HL, Miller E, Sacco RL, American Heart A, American Stroke Association Stroke C, Council on Cardiovascular S, Anesthesia, Council on Cardiovascular R, Intervention, Council on Cardiovascular N, Interdisciplinary Council on Peripheral Vascular D. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke.

2009;40(6):2276-93. doi: 10.1161/STROKEAHA.108.192218. PubMed PMID: 19423857.
30. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V. Revised Response Criteria for Malignant Lymphoma. Journal of Clinical Oncology. 2007;25(5):579-86. doi: 10.1200/JCO.2006.09.2403.

34. Mesa RA, Vannucchi AM, Mead A, Egyed M, Szoke A, Suvorov A, Jakucs J, Perkins A, Prasad R, Mayer J, Demeter J, Ganly P, Singer JW, Zhou H, Dean JP, Te Boekhorst PA, Nangalia J, Kiladjian JJ, Harrison CN. Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial. Lancet Haematol. 2017 May;4(5):e225-e236.

35. Muppidi MR, Portwood S, Griffiths EA, Thompson JE, Ford LA, Freyer CW, Wetzler M, Wang ES. Decitabine and Sorafenib Therapy in FLT-3 ITD-Mutant Acute Myeloid Leukemia. 2015 Jun;15 Suppl:S73-9.

36. Pemmaraju N, Kantarjian H, Andreeff M, Cortes J, Ravandi F. Expert Opin Investig Drugs. Investigational FMS-like tyrosine kinase 3 inhibitors in treatment of acute myeloid leukemia. 2014 Jul;23(7):943-54.

37. Ravandi F, Alattar ML, Grunwald MR, Rudek MA, Rajkhowa T, Richie MA, Pierce S, Daver N, Garcia-Manero G, Faderl S, Nazha A, Konopleva M, Borthakur G, Burger J, Kadia T, Dellasala S, Andreeff M, Cortes J, Kantarjian H, Levis M. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. Blood. 2013 Jun 6;121(23):4655-62.

APPENDIX A: Performance Status

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: Contraception

BMS defines contraception as the following:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena by WOCBP subject or male subject's WOCBP partner (previous language flexible as appropriate per Directive as based on current knowledge of effects of study drug (s) on hormone exposures and as agreed upon by MST Lead and Medical Monitor in consultation with the compound Lead Clinical Pharmacologist.). Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard
- Tubal ligation
- Vasectomy.
- Complete Abstinence*
- *Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner (inclusion flexible as appropriate per Directive as based on current knowledge of effects of study drug (s) on hormone exposures and as agreed upon by MST Lead and Medical Monitor in consultation with the compound Lead Clinical Pharmacologist)
- Female Condom*. * A male and female condom must not be used together

APPENDIX C: Concomitant Therapies Affecting Kinase Inhibitors

The following restricted therapies are permitted with caution when medically indicated. Their specific interactions with on study kinase inhibitor therapy may vary depending on the kinase inhibitor used. The use medications that affect CYP3A4 metabolism may be permitted after consultation with an oncology pharmacist.

CYP3A4 Inducers (see Table)

- Drugs that induce CYP3A4 activity may decrease kinase inhibitor plasma concentrations. In subjects in whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be used. If dasatinib, ponatinib or sorafenib must be administered with a CYP3A4 inducer, a dose increase in kinase inhibitor should be considered. If an inducer is required for subject care sunitinib may be increased to 62.5 mg daily and if tolerated for 28 days further increased to 87.5 mg daily.

CYP3A4 Inhibitors (see Table)

- Dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and drugs that inhibit CYP3A4) may increase exposure to certain kinase inhibitors. Close monitoring for toxicity and a dose reduction should be considered as listed in the tables below if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.
    - **Ponatinib may increase the blood levels and effects of PGP substrates**
    - **Dasatinib, sorafenib, pacritinib, ruxolitinib, idelalisib, and sunitinib do not cause significant changes in the blood levels of other medications.**

Common CYP3A4 Substrates

- CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in subjects receiving certain kinase inhibitors.

Common CYP2C8 Substrates

- Amiodarone, bubproprion, pioglitazone, repaglinide, rosiglitazone, and tretinoin.

Common CYP2C9 Substrates

- Carvedilol, celecoxib, dapsone, fluoxetine, fluvastatin, glimipramide, glipizide, losartan, monteleukast, nateglinide, phenytoin, sulfadiazine, sulfamethoxazole, tamoxifen, torsemide, trimethoprim, voriconazole, warfarin, zafrilukast and zopiclone.

Common 2D6 Substrates

- Amitriptyline, aripiprazole, captopril, carvedilol, codeine, desipramine, dextromethorphan, doxepin, duloxetine, flecainide, fluoxetine, haloperidol, imipramine, lidocaine, metoprolol, mexilitine, mirtazapine, nebivolol, nefazodone, nortriptyline, paroxetine, perphenazine, pindolol, procainamide, promethazine, propafenone, propranolol, risperidone, ritonavir, sertraline, tamosifen, tamsulosin, thioridazine, tolteradine, tramadol, and venlafaxine.

Common UGT1A1 Substrates

- Acetaminophen, atorvastatin, carvedilol, clofibrate, ethinylestradiol, ezetimibe, gemfibrozi, naltrexone, nicotine, simvastastin, and telmisartan.

Common PGP Substrates

- Aliskiren, colchicine, dabigatran, digoxin, everolimus, fexofenadine, marovirac, posaconazole, ranolazine, saxigliptan, sirolimus, sitagliptin, and tolvaptan.

Known Inducers & Inhibitors of CYP Isoenzymes

Inducers of CYP 3A4	
Aminoglutethamide Carbamazepine Fosphenytoin Nafcillin Nevirapine Oxcarbazepine Phenobarbital	Phenytoin Primidone Rifabutin Rifampin Rifapentine St John's wort
CYP 3A4 Inhibitors (M=Moderate, S=Strong)	
Amiodarone-M Amprenavir-S Aprepitant-M Atazanavir-S Cimetidine-M Clarithromycin-S Clotrimazole-M Conivaptan-S Cyclosporine-M Delavirdine-S Diltiazem-M Enoxacin-S Erythromycin-M Fluconazole-M Fosamprenavir-S Grapefruit juice-M/S – treat as S Imatinib-S Indinavir-S Isoniazid-S Itraconazole-S	Ketoconazole-S Metronidazole-M Miconazole-S Nefazodone-S Nelfinavir-S Nicardipine-S Norfloxacin-M Posaconazole-S Propofol-S Quinidine-S Ritonavir-S Saquinavir-M Sertraline-M Telithromycin-S Troleandomycin-M Verapamil-M Voriconazole-S

APPENDIX D: Protocol Deviations

Human Research Protection Program
Investigator Guidance

Protocol Deviations

Version 3.1
Date Effective: 7.1.2014

OREGON HEALTH & SCIENCE UNIVERSITY
Research Integrity Office
Mail code L106-RI
Portland, Oregon 97239-3098
Phone: 503-494-7887
Fax: 503-346-6808

Background:
The term "protocol deviation" is not defined by either the HHS human subjects regulations (45 CFR 46) or the FDA human subjects regulations (21 CFR 50). The federal regulations require that modifications to research occur only when prospectively approved by the IRB. Additionally, they require that all serious and continuing non-compliance is reported promptly to the IRB. Protocol deviations are a reality of the conduct of research and it is vital that they are reported to the IRB in order to assess problems in the protocol or with research management, and to make determinations of serious or continuing non-compliance.

Scope:
This policy defines the three levels of protocol deviations and the reporting and review process for deviations.

Policy:
I. It is the responsibility of the Principal Investigator not to deviate from the protocol approved by the IRB, except to avoid an immediate hazard to the subject.
II. Planned changes to the IRB-approved protocol, i.e., protocol deviations and protocol exceptions, must be submitted as formal protocol amendments (may be termed protocol exceptions if there is no change in protocol) to the IRB and must be approved prior to initiation or implementation of the change.
III. The PI will report all protocol deviations per the required reporting procedures.
IV. Any protocol deviations that meet the definition of serious and/or continuing non-compliance or unanticipated problems involving risks to subjects or others will be reported to the appropriate agencies per the policies on serious and continuing non-compliance, unanticipated problems, and institutional reporting requirements.

Procedure:
I. Reporting and Review
   A. Minor Protocol Deviations:
      1. Minor protocol deviations do not need to be reported.
      2. If a minor protocol deviation is reported, an IRB Chair or designated IRB member will review the reported deviation. The reviewer may require corrective action to be taken when there is a pattern of repeated minor protocol deviations.
      3. Minor protocol deviations that are reported to the IRB may be reviewed and resolved by one reviewer. The reviewer will generate a memo describing the resolution.
      4. If the reviewer determines that no deviation occurred, the reviewer will generate a memo to that effect.

A Phase II Proof-of-Concept Trial to Study Kinase Inhibition in Relapsed/Refractory Acute Leukemias: Using a Comprehensive In Vitro Kinase Inhibitor Panel to Select Individualized, Targeted Therapies

IRB # 7195

SUBJECT ID:_____ INITIALS:_____

APPENDIX E: Participant Eligibility Criteria

INCLUSION CRITERIA				
Each subject must meet all of the following inclusion criteria to be enrolled:				
#	**3.1 CRITERIA**	**YES**	**NO**	**Values**
3.11	Participants ≥ 18 years of age with relapsed/refractory leukemia with a confirmed diagnosis of AML or ALL, who meet the following criteria: Both men and women of all races and ethnic groups will be included. a. Individuals aged 18-64 years with salvage* treatment failures only - defined as relapsed or refractory to after least 1 cycle of salvage therapy. *Given the clinical activity and use of hypomethylating agents in AML patients, initial and salvage therapy may include hypomethylating agents.* b. Age ≥ 65 years**: Refractory to induction chemotherapy- defined as no response to ^initial therapy or have relapsed after initial therapy. **Individuals aged ≥65 years, with CMML or myelodysplasia (MDS) that transform to acute leukemia while actively receiving hypomethylating agents (i.e., decitibine or azacytidine) will be considered induction failures and are thus eligible for this trial. For Ph+ ALL, initial therapy and salvage therapy may include steroids and imatinib or dasatinib.			Date of Birth: __ __ / __ __ / __ __
3.1.2	Primary patient samples must show in vitro kinase inhibitor sensitivity as determined by the OHSU functional kinase inhibitor screen. For OHSU patients, functional kinase inhibitor screening may be performed as part			Date of assay result: __ __ / __ __ / __ __

	of this study or through enrollment in eIRB4422 if the identical FDA/CLIA approved assay is used and a result is available within 2 weeks of starting on study drug treatment.			Study drug selected: _____
3.1.3	Patients must have normal organ function as defined below: Serum creatinine < 2.0 x institutional upper limit of normal (ULN) INR < 1.5 x institutional ULN Adequate hepatic function as defined by the following criteria: Total serum bilirubin ≤1.5 x ULN, unless due to Gilbert's syndrome Alanine aminotransferase (ALT) ≤2.5 × ULN Aspartate aminotransferase (AST) ≤2.5 × ULN			Creatinine value: _____ Date: __ __ / __ __ / __ __ INR value: _____ Date: __ __ / __ __ / __ __ Serum bilirubin value: _____ Date: __ __ / __ __ / __ __ ALT value: _____ Date: __ __ / __ __ / __ __ AST value: _____ Date: __ __ / __ __ / __ __
3.1.4	ECOG performance status ≤ 2 (Karnofsky ≥ 60%, see Appendix A).			ECOG value: _____ Karnofsky Status: _____ Date: __ __ / __ __ / __ __
3.1.5	Discontinuation of anti-coagulants and anti-platelet drugs at least 7 days prior to start of study drug. Aspirin 81 mg is permitted as long as platelet count is > 50 and there is no evidence of active bleeding or coagulopathy (INR > 1.5, fibrinogen > 150.			Date anticoagulant or anti-platelet discontinued: __ __ / __ __ / __ __
3.1.6	No uncontrolled infections as determined by the investigator			
3.1.7	No clinically significant thyroid disease (e.g. hyperthyroid/hypothyroidism)			

3.1.8	No active GVHD: Patients with a history of stem cell transplant are eligible but cannot have evidence of active GVHD as determined by the investigator.			
3.1.9	Must be able to take oral medication.			
3.1.10	Women of childbearing potential must have a negative serum or urine pregnancy test (sensitivity < 25 IU HCG/L) within 72 hours prior to the start of study drug.			Date pregnancy test: __ __/___/__ __ Time pregnancy test: __ __ : __ __ (24 clock)
3.1.11	Persons of reproductive potential must agree to use an adequate method of contraception throughout treatment and for at least 4 weeks after study drug is stopped. Women of childbearing potential and men with a sexual partner of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.			Type of Contraception: _____ _____
3.1.12	Ability to understand and the willingness to sign a written informed consent and HIPAA document.			
3.1.13	Serum Na, K, Mg, and total serum Ca or ionized Ca levels must be greater than or equal to the institutional lower limit of normal. Subjects with low K or Mg levels, total corrected serum Ca and/or ionized Ca must be replete for protocol entry.			Date: __ __/__ __/__ __ Na value: _____ K value: _____ Mg value: _____ Serum Ca value: _____ Ionized Ca value: _____

DRUG SPECIFIC INCLUSION CRITERIA

Each subject must meet the specific inclusion criteria to be administered a specific study drug:

Drug	CRITERIA	YES	NO	VALUES
Ponatinib	Female and male patients who are fertile must agree to use an effective form of contraception with their sexual partners from randomization through 4			

	months after the end of treatment.			
	Discontinuation of any medications known to contribute significantly to the risk of QT prolongation at least 48 hours prior to start of study drug. Levaquin and Zofran are an exception. Of note, certain agents that prolong the QTc may be allowed but only after discussion with the chemotherapy pharmacist. Should the investigator believe that therapy with a potentially QT prolonging medication is vital to an individual subject's care, then additional ECGs should be done at the investigator's discretion to ensure the subject's safety.			QT prolongation medication: _____ Date Discontinued: __ __ / __ __ / __ __
	Serum lipase and amylase ≤1.5 × ULN			Serum lipase value: _____ Date: __ __ / __ __ / __ __ Serum Amylase value: _____ Date: __ __ / __ __ / __ __
Dasatinib	Discontinuation of any medications known to contribute significantly to the risk of QT prolongation at least 48 hours prior to start of study drug. Levaquin and Zofran are an exception. Of note, certain agents that prolong the QTc may be allowed but only after discussion with the chemotherapy pharmacist. Should the investigator believe that therapy with a potentially QT prolonging medication is vital to an individual subject's care, then additional ECGs should be done at the investigator's discretion to ensure the subject's safety.			QT prolongation medication: _____ Date Discontinued: __ __ / __ __ / __ __

	Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.			
	Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 90 days (duration of sperm turnover) for a total of 90 days post-treatment completion.			
	Azoospermic males and WOCBP, who are not heterosexually active, are exempt from contraceptive requirements. However, WOCBP must still under pregnancy testing as described in this section.			
	Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective contraception. Highly effective methods of contraception have a failure rate of <1% when used consistently and correctly.			
	At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below.			
Sorafenib	Creatinine <1.5 X ULN			Creatinine: _____ Date: __ __ / __ __ / __ __

Pacritinib	Discontinuation of any medications known to contribute significantly to the risk of QT prolongation at least 48 hours prior to start of study drug. Levaquin and Zofran are an exception. Of note, certain agents that prolong the QTc may be allowed but only after discussion with the chemotherapy pharmacist. Should the investigator believe that therapy with a potentially QT prolonging medication is vital to an individual subject's care, then additional ECGs should be done at the investigator's discretion to ensure the subject's safety.			

EXCLUSION CRITERIA

Each subject must not meet any of the following exclusion criteria:

	3.3 CRITERIA	YES	NO	VALUES
3.3.1	Any leukemia treatment within 1 week (for cytotoxic therapy) and/or 5 half lives (for targeted agents) prior to starting study drug. Corticosteroids are allowable throughout the study to treat concomitant medical disorders per provider discretion. Hydroxyurea is allowed prior to enrollment and after the start of the study drug for the control of peripheral leukemic blasts in subjects with leukocytosis per physician discretion.			Chemotherapy, radiotherapy, immunotherapy or investigational agent: _____ Date Discontinued: __ __ / __ __ / __ __
3.3.2	Recent uncontrolled angina, recent >NYHA class III congestive heart failure, or recent MI (within 6 months) prior to start of study treatment.			Description: _____ _____
3.3.3	Diagnosed congenital long QT syndrome			Date of Dx: __ __ __ __ / __ __ __ __
3.3.4	Any recent history of clinically significant			Description:

	ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsade's de pointes).			_____ _____
3.3.5	History of clinically significant bleeding disorder unrelated to cancer.			Description: _____
3.3.6	Drugs that affect the CYP3A4 system (inducers/inhibitors/substrates) are allowed but should be used with caution (see appendix D) depending on specific kinase inhibitor used. Dietary supplements will be discouraged; however, their use may be allowed on a case by case basis per the discretion of the investigator after consultation with an oncology pharmacist.			
3.3.7	Uncontrolled intercurrent illness that would limit compliance with study requirements.			
3.3.8	Pregnant or lactating women are excluded from this study because of possible risk to the fetus or infant			
3.3.9	Known HIV-positive patients are excluded from the study because of possible risk of lethal infection when treated with marrow suppressive therapy.			Date of dx: __ __ / __ __ / __ __
3.3.10	History of hypersensitivity to any of the kinase inhibitors included in this study.			

DRUG SPECIFIC EXCLUSION CRITERIA				
Each subject must not meet any of the following exclusion criteria for each specific study drug:				
Drug	**CRITERIA**	**YES**	**NO**	**VALUES**
Ponatinib	History of acute pancreatitis within 1 year of study or history of chronic pancreatitis			Date of Dx: __ __ / __ __ / __ __
	QTC >450 msec for men and > 470 msec for women.			QTcB: _____ Dates of ECG: __ __ / __ __ / __ __

	Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL)			
	Any history of myocardial infarction, stroke, or revascularization.			Date of Dx: __ __ / __ __ / __ __ Description: _____
	Any history of venous thromboembolism including deep venous thrombosis or pulmonary embolism.			Date of Dx: __ __ / __ __ / __ __
	Unstable angina or transient ischemic attack within 6 months prior to start of study treatment.			Date of Dx: __ __ / __ __ / __ __
	History of clinically significant (as determined by the treating physician) atrial arrhythmia.			Date of Dx: __ __ / __ __ / __ __
	Congestive hear failure within 6 months prior to enrollment, or left ventricular ejection fraction (LVEF) less than lower limit of normal per local institutional standards within 6 months prior to enrollment.			Date of Dx: __ __ / __ __ / __ __
	Uncontrolled hypertension (diastolic blood pressure >90 mm Hg; systolic >140 mm Hg). Patients with hypertension should be under treatment on study entry to effect blood pressure control.			BP:
	History of ongoing alcohol abuse.			
	Ocular toxicity present as measure during a comprehensive eye exam.			Date of Exam: __ __ __ / __ __ __ / __ __ __
Dasatinib	Known pulmonary arterial hypertension			Date of Dx: __ __ __ / __ __ __ / __ __ __
	Patients may not have a clinically			Date of Dx:

	significant pleural or pericardial effusion.			__ __ / __ __ / __ __
	Uncontrolled hypertension: inability to maintain blood pressure below the limit of 140/90mgHg.			
	Any history of second or third degree heart block (may be eligible of the subject currently has a pacemaker)			
	Prolonged QTc interval (>450 msec for men and >470 msec for women) on pre-entry electrocardiogram.			Date of Sx/Bx/traumatic injury: __ __ / __ __ / __ __
Sorafenib	Non-healing wound, ulcer, or bone fracture.			
	Thrombotic or embolic venous or arterial events, such as cerebrovascular accident, including transient ischemic attacks, arterial thrombosis, deep vein thrombosis and pulmonary embolism within the past 6 months Line associated DVTs which are adequately treated (line removed and/or patient anticoagulated).			
	Uncontrolled hypertension.			
	Active bleeding during screening.			
	Major surgery, open biopsy, or significant traumatic injury within 30 days.			
Idelalisib	Ongoing drug-induced liver injury, chronic active hepatitis C (HCV), chronic active hepatitis B (HBV), alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis,			

	cirrhosis of the liver, portal hypertension, or history of autoimmune hepatitis.			
	Ongoing symptomatic pneumonitis.			
	Ongoing inflammatory bowel disease or autoimmune colitis.			
	Ongoing CMV infection, treatment, or prophylaxis within the past 28 days prior to the screening test for active CMV.			
	History of serious allergic reaction including anaphylaxis and epidermal necrolysis.			
Ruxolitinib	Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or risk of reactivation: HBV DNA and HCV RNA must be undetectable. Subjects cannot be positive for hepatitis B surface antigen (HBsAg) or anti–hepatitis B core antibody. Subjects who have positive anti-HBs as the only evidence of prior exposure may participate in the study provided that there is both 1) no known history of HBV infection, and 2) verified receipt of hepatitis B vaccine.			
Pacritinib	Major surgery, open biopsy, or significant traumatic injury within 30 days.			
	Active bleeding during screening.			
	QTC >450 mSec for men and > 470 msec for women.			

	NYHA Class II Congestive Heart Failure (a history of CHF is allowed as long as this has resolved to < NYHA Class II within 30 days of initiation of pacritinib.			

ELIGIBILITY SUMMARY

☐ Eligible

☐ Ineligible, subject is a screen fail

☐ Ineligible, waiver granted

If waiver granted, list criteria and rationale:

INVESTIGATOR NAME	
INVESTIGATOR SIGNATURE	
DATE	

PARTICIPANT REGISTRATION

Date Screening Consent Signed	__ __ / __ __ / __ __	
Meets Eligibility Inclusion/Exclusion	☐ Yes ☐ No	__ __ / __ __ / __ __
ECOG/Karnofsky Score Assessed	☐ Yes ☐ No	__ __ / __ __ / __ __
Vitals Assessed	☐ Yes ☐ No	__ __ / __ __ / __ __
Pregnancy test performed?	☐ Yes ☐ No ☐ NA	__ __ / __ __ / __ __
Bone marrow exam completed	☐ Yes ☐ No ☐ NA	__ __ / __ __ / __ __
Skin biopsy sent to central lab	☐ Yes ☐ No ☐ NA	__ __ / __ __ / __ __
PK assessment performed?	☐ Yes ☐ No	__ __ / __ __ / __ __
Chest X-ray	☐ Yes ☐ No	__ __ / __ __ / __ __
ECG (12 lead)	☐ Yes ☐ No	__ __ / __ __ / __ __
Chemistry performed (sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, total bilirubin, ALT, AST, total protein, alkaline phosphatase, uric acid, calcium, Lactate dehydrogenase (LDH), phosphorus, magnesium)	☐ Yes ☐ No	__ __ / __ __ / __ __
CBC w/ extended differential performed	☐ Yes ☐ No	__ __ / __ __ / __ __
INR/PTT Performed?	☐ Yes ☐ No	__ __ / __ __ / __ __
Study Drug Selected for Treatment	☐ Sorafenib ☐ Ponatinib ☐ Sunitinib ☐ Dasatinib ☐ Ruxolitinib ☐ Idelalisib	