PROTOCOL

TITLE:	A Multicenter Open-Label Phase 2a Study of Ibrutinib Monotherapy or in Combination with either Cytarabine or Azacitidine in Subjects with Acute Myeloid Leukemia
PROTOCOL NUMBER:	PCYC-1131-CA
STUDY DRUG:	IMBRUVICA® (ibrutinib)
IND NUMBER:	102,688
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DATE FINAL:	08 August 2014
AMENDMENT 1:	15 January 2016

PROTOCOL APPROVAL PAGE

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I have carefully read Protocol PCYC-1131-CA entitled "A Multicenter Open-Label Phase 2a Study of Ibrutinib Monotherapy or in Combination with either Cytarabine or Azacitidine in Subjects with Acute Myeloid Leukemia". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Pharmacyclics, and the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Pharmacyclics. All data pertaining to this study will be provided to Pharmacyclics.
The policy of Pharmacyclics LLC requires that any presentation or publication of study data by clinical Investigators be reviewed by Pharmacyclics, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

The following Pharmacyclics LLC representative is authorized to sign the protocol and any amendments:

Medical Monitor's Signature Date
Nora Marie Cavazos, MD
Clinical Development, Pharmacyclics LLC

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SYNOPSIS

Study Title:	A Multicenter Open-Label Phase 2a Study of Ibrutinib Monotherapy or in Combination with either Cytarabine or Azacitidine in Subjects with Acute Myeloid Leukemia
Protocol Number:	PCYC-1131-CA
Study Phase:	2a
Study Duration:	Estimated to be 3.5 – 4 years
Investigational Product and Reference Therapy:	Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. Low-dose cytosine arabinoside (LD-AraC) will be administered at 20 mg twice daily (BID) subcutaneously (sc) for 10 days of a 28-day cycle. Azacitidine will be administered at 75 mg/m^2 intravenously (IV) once daily on Days 1-7 of a 28-day cycle (with an option to increase to 100 mg/m^2 IV once daily after 2 cycles).
Objectives:	**Primary Objectives:** • To evaluate the efficacy of ibrutinib monotherapy or in combination with either LD-AraC or azacitidine in the treatment of Acute Myeloid Leukemia (AML) using the overall remission rate (defined as proportion of subjects achieving a CR or CRi) according to the LeukemiaNet guidelines (Döhner 2010) • To evaluate the safety and tolerability of ibrutinib monotherapy or in combination with either LD-AraC or azacitidine in subjects with AML **Secondary Objectives:** • To evaluate clinical efficacy by assessing relapse-free survival (RFS), event-free survival (EFS), and overall survival (OS) • To evaluate clinical benefit defined as complete remission (CR), complete remission with incomplete marrow recovery (CRi), morphologic leukemia-free state, or partial remission (PR) **Exploratory Objectives:** • To determine the plasma pharmacokinetics (PK) of ibrutinib monotherapy or in combination with either LD-AraC or azacitidine in an AML population • To evaluate prognostic and predictive biomarkers relative to treatment outcomes (ie, Btk/pBtk, secreted proteins, gene expression profiling, mutational analysis)
Study Design:	This Phase 2a open-label, non-randomized U.S. multicenter study is designed to evaluate the safety and efficacy of ibrutinib monotherapy or in combination with either cytarabine or azacitidine in the treatment of subjects with AML. A maximum of 101 response evaluable subjects will be enrolled in up to 3 treatment cohorts: • Cohort 1 – ibrutinib monotherapy: ibrutinib 560 mg once daily on a

	continuous basis. • Cohort 2 – ibrutinib + LD-AraC: ibrutinib 560 mg once daily on a continuous basis plus low dose cytarabine. • Cohort 3 – ibrutinib + azacitidine: ibrutinib 560 mg once daily on a continuous basis plus IV azacitidine. The study will begin with a safety run-in in the ibrutinib + LD-AraC combination cohort only. Six subjects will receive ibrutinib at a dose level of 560 mg once daily on a continuing basis starting 2 days prior to the first cytarabine dose. LD-AraC will be administered at 20 mg twice daily (BID) subcutaneously (sc) for 10 days of a 28-day cycle. Assessment for dose limiting toxicities (DLTs) will continue for the first treatment cycle. Refer to Section 5.2. If 2 of the first 6 subjects experience DLTs, 3 additional subjects will be assessed for DLT(s). If 3 or more of the 9 subjects experience DLTs, enrollment will be halted at the 560 mg dose level. At Sponsor's discretion a dose of 420 mg ibrutinib or lower (plus LD-AraC) may be explored. If less than 2 out of 6 subjects or less than 3 out of 9 subjects experience DLT(s), additional subjects will be enrolled in one of two treatment cohorts: • Cohort 1: ibrutinib monotherapy: up to 33 response evaluable subjects will receive ibrutinib 560 mg once daily on a continuous basis. OR • Cohort 2: ibrutinib + LD-AraC: up to 25-28 additional response evaluable subjects (for a total of 34 subjects) will receive ibrutinib 560 mg once daily on a continuous basis starting 2 days prior to first cytarabine dose (20 mg BID sc) for 10 days of a 28-day cycle. Subjects will be assigned to either treatment cohort at the discretion of the treating investigator. Efficacy parameters will be monitored closely. In the event response assessments suggest futility in the ibrutinib + AraC cohort, further enrollment in either the ibrutinib monotherapy or the ibrutinib + AraC cohorts will be closed and a new cohort of ibrutinib + azacitidine will be started: • Cohort 3: ibrutinib + azacitidine: up to 34 response evaluable subjects will receive ibrutinib 560 mg once daily on a continuous basis starting 1 day prior to first azacitidine dose + azacitidine 75mg/m^2 IV once daily Days 1-7 of a 28-day cycle (with an option to increase to 100 mg/m^2 after 2 cycles). For Cohort 3 the same safety run-in principle as Cohort 2 (6+3 design) will be implemented. If less than 2 out of 6 subjects or less than 3 out of 9 subjects experience DLT(s), additional subjects will be enrolled. If 3 or more of the 9 subjects experience DLTs, enrollment will be halted at the 560 mg dose level. At Sponsor's discretion a dose of 420 mg ibrutinib or lower (plus azacitidine) may be explored. Study treatment will continue in subjects who demonstrate a PR or better

	on their Cycle 2 Day 1 bone marrow assessment according to the LeukemiaNet guidelines (Döhner 2010) or based on clinical benefit as determined by the treating physician. Treatment may continue thereafter until unacceptable toxicity, treatment failure (TF), or withdrawal of consent. Subjects treated in the ibrutinib monotherapy cohort who experience a documented TF or relapse will be permitted to add LD-AraC to ibrutinib per investigator discretion.
Population:	Adult subjects with pathologically documented AML that have failed standard treatment, or subjects without prior therapy who refuse standard chemotherapy
Centers:	Approximately 10-15 US centers

Inclusion Criteria:
 	
Refer to Section 4 *for the complete and detailed list of inclusion/exclusion criteria.*
	• Male and female ≥18 years of age.
	• Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
	• Subjects with pathologically documented AML that has failed standard treatment (based on NCCN guidelines), or subjects without prior therapy who refuse standard treatment options
	• Screening bone marrow aspirate/biopsy results showing >5% blasts.
	• WBC count <25,000 cells/mm^3 (25 x 10^9/L).
	  ○ The use of hydroxyurea (HU) during the screening phase is permitted to control the peripheral blood count until 1 day (~5 half lives) prior study treatment.
	• Platelet count >10,000 cells/mm^3 (10 x 10^9/L).
	• Adequate hepatic and renal function defined as:
	  ○ For Cohorts 1 and 2: Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤3.0 x upper limit of normal (ULN); for Cohort 3: ALT ≤2.5 or AST ≤2.5 x ULN
	  ○ Serum creatinine ≤2 mg/dL or Estimated Creatinine Clearance ≥30 mL/min (Cockcroft-Gault)
	  ○ Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
	• PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). When treated with warfarin or other vitamin K antagonists, then INR ≤3.0).

Exclusion Criteria: *Refer to* Section 4 *for the complete and detailed list of inclusion/exclusion criteria.*	• Acute promyelocytic leukemia (French-American-British Class M3 AML) • Known active central nervous system (CNS) leukemia • Known active systemic infection (Grade ≥2) • Clinical signs of bleeding (Grade ≥2) • Prior treatment with a BTK inhibitor • For Cohort 3 subjects, prior treatment with hypomethylating agents

	• Prior bone marrow transplant that requires immunosuppressant therapy or presents with graft vs host disease (GVHD) • Anticancer therapy including chemotherapy, immunotherapy, radiotherapy, hormonal or any investigational therapy within 14 days or 5 half-lives (whichever is shorter) prior to first dose of study drug. • Subject has received a monoclonal antibody for anticancer intent within 8 weeks prior to the first dose of study drug. • Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug. • Recent infection requiring intravenous (IV) systemic treatment that was completed ≤14 days before the first dose of study drug. • Known bleeding disorders (eg, von Willebrand's disease) or hemophilia. • History of stroke or intracranial hemorrhage within 6 months prior to enrollment. • Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. • Major surgery within 4 weeks of first dose of study drug. • Concomitant use of warfarin or other Vitamin K antagonists. • Requires treatment or prophylaxis with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix 5) • Currently active, clinically significant hepatic impairment (≥ moderate hepatic impairment according to the Child Pugh classification [Appendix 7]). • Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations)
Study Treatment:	Cohort 1 – ibrutinib monotherapy: ibrutinib 560 mg once daily on a continuous basis Cohort 2 – ibrutinib + AraC: ibrutinib 560 mg once daily on a continuous basis starting 2 days prior to first cytarabine dose (20 mg BID sc) for 10 days of a 28-day cycle Cohort 3 –ibrutinib + azacitidine: ibrutinib 560 mg once daily on a continuous basis starting 1 day prior to first azacitidine dose + azacitidine 75 mg/m^2 IV once daily on Days 1-7 of a 28-day cycle (with an option to increase to 100 mg/m^2 after 2 cycles).
Concomitant Therapy:	*Refer to Section 6 for information on concomitant therapy.*
Safety Plan:	A safety review will be conducted for Cohort 2 (ibrutinib + AraC) after the first 6-9 subjects have completed the first cycle of treatment. A safety review will be conducted for Cohort 3 (ibrutinib + azacitidine) after the first 6-9 subjects have completed the first cycle of treatment.

	The study will be monitored in accordance to the Sponsor's Pharmacovigilance procedures. Adverse events and serious adverse events (SAEs) will be reviewed internally on an ongoing basis to identify safety concerns.
Statistical Methods and Data Analysis:	**Primary Efficacy Analysis:** Overall remission rate (ORR) is defined as the proportion of response evaluable subjects who achieve a complete remission (CR) or complete remission with incomplete marrow recovery (CRi). The ORR along with its 95% exact binomial confidence interval will be presented for each cohort separately. Response evaluable subjects are defined as subjects who had at least 1 post-baseline response assessment or any subjects who died due to an AML-related cause or were discontinued early due to an AML-related event without at least 1 post-baseline response assessment. **Secondary Efficacy Analyses:** Secondary efficacy variables including relapse-free survival (RFS), event-free survival (EFS), overall survival (OS), and clinical benefit rate (CBR) will be analyzed. The efficacy of two treatment cohorts (ibrutinib monotherapy and ibrutinib with LD-AraC) will be evaluated separately. No multiplicity adjustment will be applied to the analysis. **Safety Analysis:** Analysis of safety data will be conducted on the all treated population, which includes enrolled subjects who receive at least 1 dose of study drug (ibrutinib). All subjects are to be monitored for adverse events during the study. Other safety measurements include clinical laboratory tests and vital signs. Descriptive statistics for each cohort will be used to summarize safety data (adverse events [AEs], clinical laboratory tests and vital signs) for all subjects receiving the study drug. Summary statistics will include incidence, means, standard deviations, and medians for continuous variables and proportions for categorical variables.
Interim Analysis	No formal interim analysis is planned.
Sample Size Determination	Sample size was calculated to detect a meaningful signal of activity of each treatment cohort while minimizing risk of continuing enrollment under null conditions. The sample size was estimated for each treatment cohort without multiplicity adjustment. The study will enroll up to 33 response evaluable subjects in the monotherapy cohort and up to 34 response evaluable subjects in each of the for combination cohorts. The sample size of 33 subjects was calculated to test the null hypothesis that the ORR of ibrutinib monotherapy is ≤5% (not clinically compelling) versus the alternative hypothesis that ORR will be ≥20%, with a significance level of 5%, and 80% power. The sample size of 34 subjects was calculated to test the null hypothesis that the ORR of ibrutinib plus LD-AraC or ibrutinib plus azacitidine is ≤15% (not clinically compelling) versus the alternative hypothesis that ORR will be ≥35%, with a significance level of 5%, and 80% power.

ABBREVIATIONS

AEs	adverse events
AESI	Adverse events of special interest
ANC	absolute neutrophil count
AML	Acute myeloid leukemia
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
AUC	area under the curve
BCR	B-cell receptor
BID	twice daily
BMSCs	bone-marrow stromal cells
BR	bendamustine and rituximab
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBR	clinical benefit rate
CFR	Code of federal regulation
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CNS	central nervous system
CR	complete remission
CRF	case report form (paper or electronic as appropriate for this study)
CRi	complete remission with incomplete marrow recovery
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Event
CV	coefficient of variation
CYP	cytochrome P450
DLTs	dose limiting toxicities
ECG	Electrocardiogram
eDC	electronic data capture
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EOT	End-of-treatment visit
FDA	U.S. Food and Drug Administration
FCR	fludarabine, cyclophosphamide, and rituximab
GCP	Good Clinical Practice
GVHD	Graft vs. Host disease
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus

HU	Hydroxyurea
IB	Investigator's Brochure
IC_{50}	concentration that inhibits a process by 50%
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normal ratio
IRB	Institutional Review Board
IUDs	intrauterine devices
IV	Intravenous
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LD-AraC	low-dose cytarabine
LDH	lactate dehydrogenase
LTFU	Long-term follow up
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	overall remission rate
OS	overall survival
pBTK	Bruton's tyrosine kinase protein
PCR	polymerase chain reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PML	progressive multifocal encephalopathy
PO	for oral
PR	partial remission
PT	prothrombin time
QTc	corrected QT interval
RFS	relapse-free survival
RFU	response follow up
R-CHOP	rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone
SAEs	serious adverse events
sc	Subcutaneous
SJS	Stevens-Johnson Syndrome
SLL	small lymphocytic lymphoma
$t_{1/2}$	half life
T_{max}	time to maximum plasma concentration
TF	treatment failure
TLS	tumor lysis syndrome
ULN	upper limit of normal
WBC	White blood cell
WHO	World Health Organization

1. BACKGROUND

1.1. Acute Myeloid Leukemia (AML)

Acute myeloid leukemia (AML) is characterized by the proliferation and accumulation of myeloid progenitor cells in the bone marrow, which leads to hematopoietic failure (Robak 2009). AML is the most frequent acute leukemia in adults and its incidence increases with age. An estimated 18,860 people will be diagnosed with AML in 2014 in the U.S. and 10,460 will die of the disease (Siegel 2013). The median age at diagnosis is 66 years, with 54% of patients diagnosed at 65 years or older and approximately a third diagnosed at 75 years of age or older (Yin 2012). Causes of AML include chemical exposure, prior chemotherapy and radiation, as well as other environmental toxins. Of all the leukemias, AML has the lowest survival rate particularly in elderly subgroups as a result of poorer tolerability to standard therapy and the fact that elderly patients more frequently present with poor prognostic features.

In 2008 the World Health Organization (WHO) revised the diagnostic and response criteria for AML, which was based on cytochemical stains and morphology, to include additional recurrent genetic abnormalities and molecular markers that appear to have prognostic impact. In the past 5 years the presence of autosomal monosomies (5 and 7) was found to be associated with decreased overall survival in patients aged 60 years and older. Molecular profiling is increasing the ability to identify mutations that carry prognostic impact, particularly in patients with normal karyotype. Markers that have been incorporated into risk categorization include FMS-like tyrosine kinase 3 (FLT3), c-KIT, nucleophosmin (NPM1) and CEBPA gene mutations. Molecular genetics is a rapidly evolving field in AML, and risk stratification is modified based on continuous evaluation of evolving data.

1.1.1. Treatment Options

Treatment of acute leukemia consists of induction chemotherapy and post-remission therapy. Standard induction therapies in patients younger than 60 years are based on high dose cytarabine and/or anthracyclines, with remission rates of 60%–70% and cure rates of 15%–25%. Post remission treatments consist of 3–4 cycles of high dose cytarabine regimens. Despite the use of higher doses of cytarabine or addition of other chemotherapy agents (eg, etoposide, fludarabine) to the standard combination, the median progression-free survival is only approximately 7 months and most patients with AML will still succumb to their disease (Kern 2006).

Treatment of AML in first relapse is associated with relatively low response rates. Whenever second complete remission (CR) is attained, the median duration of the second relapse-free interval is generally considerably shorter compared to the first response (Leopold 2002). Patients failing to respond to one or two cycles of induction treatment may be considered for allogeneic stem cell transplantation if an HLA-matched donor is available. For patients who emerge from the induction phase in poor condition to tolerate active treatment, best supportive care is provided. Because only a minority of the patients who are refractory or experience

relapse will derive durable benefit from re-induction therapy, relapsed or refractory AML remains a field of high unmet need for new therapeutic options.

Several studies suggest that elderly patients are often not offered standard induction chemotherapy given that early treatment related mortality can be in the range of 30% (Tilly 1990). Median survival in patients 60 years of age or older is approximately 2 years and the overall cure rate is <20% (Menzin 2002). The creation of separate guidelines for patients older than 60 recognizes their poor outcomes associated with an increased proportion of unfavorable karyotypes and mutations with multidrug resistance, as well as treatment-related mortality that exceeds any expected response in this age group (Appelbaum 2006). For patients who cannot tolerate standard induction or intermediate intensity treatment, the NCCN guidelines (AML, Version 1 2015) options for low-intensity treatments include subcutaneous low-dose cytarabine, azaditidine and decitabine. Studies of these treatments in treatment naïve patients unfit for chemotherapy have demonstrated CR rates between 18% and 35%, and disease free survival in patients who achieved CR of approximately 8 months (Burnett 2007, Fenaux 2010, Cashen 2010). There is an urgent need to identify treatment strategies for AML which are not only effective but can be tolerated by older, relatively unfit patients.

The use of ibrutinib as a potent covalent BTK inhibitor for the treatment of AML has not yet been investigated and may represent a safe and effective addition to the therapeutic arsenal. Moreover, the favorable toxicity profile of ibrutinib lends itself well to combination trials with the standard chemotherapeutic agents and potentially other targeted agents of interest in AML.

1.1.2. Role of Bruton Tyrosine Kinase (BTK) in Acute Myeloid Leukemia

Bruton tyrosine kinase (BTK) is an essential mediator in B lymphocytes coupling activated immunoreceptors to downstream signaling events that affect diverse biological functions, from cellular proliferation, differentiation and adhesion to innate and adaptive immune responses in the treatments of B cell malignancies such as chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) (Byrd 2013, Wang 2013), and is also an attractive potential approach for autoimmune diseases and inflammatory disorders (Honigberg 2010, Chang 2011).

While BTK plays an important role in BCR-mediated signaling in the B-cell lineage, it is also expressed in other hematopoietic cell types such as monocytes/macrophages and neutrophils and contributes to immune-complex mediated activation of the FcγR signaling pathway as well as in TLR systems in these cells.

Studies in AML derived cell lines suggest a role for BTK as a potential therapeutic target in AML (Rushworth 2014). BTK phosphorylation (at Y223 and possibly Y551) was identified in AML blasts and ibrutinib was able to occupy the active site of BTK in AML cells with equivalent efficiency as it does in CLL. The majority of the primary AML blasts displayed therapeutic responses to the BTK inhibitor ibrutinib on cell growth, adhesion and colony formation. In addition, ibrutinib augmented the cytotoxic effects of both cytarabine and daurorubicin to BTK expressing AML cells in colony forming assays.

AML cell lines pretreated with ibrutinib at concentrations achievable in vivo and subsequently exposed to SDF1 (stromal derived factor 1) demonstrated CXCR4-mediated inhibition of cell migration compared to untreated controls (Zaitseva 2014), a mechanism that has been previously reported for CLL and other B-cell malignancies.

BTK-dependent signaling has been shown to be highly context-dependent. In FLT3-ITD-positive AML, BTK mediates FLT3-ITD dependent activation. Combined targeting of FLT3-ITD and BTK using various concentrations of quizartinib and ibrutinib demonstrated an additive anti-proliferative effect (Oellerich 2015).

1.2. Investigational Product Name and Description

Ibrutinib (IMBRUVICA ®) is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK) developed by Pharmacyclics LLC for the treatment of B-cell malignancies.

Ibrutinib has been approved in many regions, including the US and EU, for indications covering the treatment of patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) who has received at least 1 prior therapy, first-line treatment of patients with CLL with a deletion of the short arm of chromosome 17 (del17p) or a *TP53* mutation, and patients with Waldenström's macroglobulinemia. Ibrutinib is currently under investigation in various indications as a single agent and in combinations.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop 2003).

For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of ibrutinib, refer to the latest version of the ibrutinib Investigator's Brochure (IB).

1.3. Summary of Nonclinical Data

1.3.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the BTK (Pan 2007). In vitro, ibrutinib is a potent inhibitor of BTK activity (IC_{50} = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of BTK results in sustained inhibition of BTK catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the BCR

and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011).

Ibrutinib arrested cell growth and induced apoptosis in human B-cell lymphoma cell lines in vitro and inhibited tumor growth in vivo in xenograft models (Herman 2011). Ibrutinib also inhibited adhesion and migration of MCL cells in co-culture and reduced tumor burden in lymph node and bone marrow in a murine model of MCL dissemination and progression (Chang 2013a, Chang 2013b).

For more detailed and comprehensive information regarding nonclinical pharmacology and toxicology, please refer to the current IB.

1.3.2. Safety Pharmacology and Toxicology

No treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs. Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

In studies in pregnant rats and rabbits, ibrutinib administration was associated with malformations (teratogenicity) at ibrutinib doses that result in approximately 14 and 2 times the exposure (AUC) in patients administered the dose of 560 mg daily, respectively. Fetal loss and reduced fetal body weights were also seen in treated pregnant animals.

Carcinogenicity studies have not been conducted with ibrutinib. In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. No effects on fertility or reproductive capacities were observed in a study in male and female rats.

For the most comprehensive information regarding nonclinical safety pharmacology and toxicology, please refer to the current IB.

1.4. Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, please refer to the current version of the IB.

1.4.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally to doses increased with substantial intersubject variability.

The mean half life ($t_{1/2}$) of ibrutinib ranged from 4 to 13 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

For the most comprehensive information regarding pharmacokinetics (PK) and product metabolism, please refer to the current version of the IB.

1.5. Summary of Clinical Safety

A brief summary of safety data from monotherapy and combination therapy studies is provided below. For more comprehensive safety information please refer to the current version of the IB. Additional safety information may be available for approved indications in regional prescribing labels where the study is conducted (eg, USPI, SmPC).

1.5.1. Monotherapy Studies

Pooled safety data for total of 1071 subjects treated with ibrutinib monotherapy from 9 studies in B-cell malignancies, which includes subjects from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy, are summarized below.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1071):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
Pyrexia	Atrial fibrillation	
Neutropenia		

1.5.2. Combination Studies

Pooled safety data for a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in B-cell malignancies, which included 1 randomized-control study, are summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=423):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Neutropenia	Neutropenia	Febrile neutropenia
Diarrhea	Thrombocytopenia	Pneumonia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Hypertension	

1.5.3. Risks

1.5.3.1. Bleeding-related Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 6.2.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.4 for guidance on ibrutinib management with surgeries or procedures.

At this time there are no data available to describe or predict how ibrutinib will affect the circulating levels of myeloid blasts.

1.5.3.2. Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.4.1.4).

1.5.3.3. Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib.

1.5.3.4. Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.4.1.4).

1.5.3.5. Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE v4.03). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib.

1.5.3.6. Second primary Malignancies

Second primary malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib. Second primary malignancies including non-skin carcinomas have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer.

1.5.3.7. Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity.

1.5.3.8. Lymphocytosis and Leukostasis

Leukostasis

There were isolated cases of leukostasis reported in subjects with CLL and NHL treated with ibrutinib. A high number of circulating lymphocytes (>400,000/µL) may confer increased risk.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5000/µL), often associated with reduction of lymphadenopathy,

has been observed in most subjects with CLL/ small lymphocytic lymphoma (SLL) treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

A large increase in the number of circulating lymphocytes (eg, >400,000/µL) has been observed in some subjects. Lymphocytosis was not observed in subjects with Waldenström's macroglobulinemia treated with ibrutinib. Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving ibrutinib in combination with chemoimmunotherapy.

At this time there are no data available to describe or predict how ibrutinib will affect the circulating levels of myeloid blasts.

1.5.3.9. Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of TLS are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities**.**

1.6. Summary of Clinical Data

This is the first clinical study of ibrutinib in subjects with AML.

1.7. Study Rationale

The study will enroll adult subjects with pathologically documented AML who have failed standard treatment, or subjects without prior therapy who cannot tolerate or refuse standard chemotherapy. Subjects will receive ibrutinib monotherapy or in combination with either low-dose cytarabine (LD-AraC) or azacitidine. LD-AraC and hypomethylating agents (azacitidine and decitabine) are recommended by the NCCN guidelines for patients who are deemed unfit for standard induction or intermediate-intensity therapy. Low dose cytarabine resulted in a survival benefit and a CR rate of 18% vs. 1% compared to hydroxyurea in newly diagnosed AML older patients with favorable or normal karyotype (Burnett 2007). Azacitidine was compared to conventional care (Fenaux 2010) in high risk MDS and AML showed a significant survival benefit in favor of azacitidine in patients with AML. Even with the low intensity treatment approach overall prognosis remains poor for older patients.

Studies with AML patient-derived blasts and established AML cell lines suggested BTK as a potential therapeutic target in AML (Rushworth 2014). Primary AML cells had increased levels of BTK phosphorylation at tyrosine-223 (the auto-phosphorylation site) compared to $CD34^+$ immature hematopoietic cells derived from healthy volunteers, suggesting BTK activity is elevated in AML cells. Ibrutinib was able to bind BTK in AML cells comparably as it does in CLL cells. The majority of patient-derived AML blasts were inhibited by ibrutinib in cell growth assays including clonogenic colony formation in soft agar. Furthermore, ibrutinib augmented the cytotoxic effects of both cytarabine and daurorubicin to BTK-expressing AML cells in colony formation assays. Importantly, there was an association of ibrutinib inhibition in growth assays with the level of BTK phosphorylation, suggesting that BTK inhibition by ibrutinib has a direct impact on AML cell proliferation.

Another key element for the efficacy of ibrutinib in human AML patients is its potential impact on cell adhesion to the bone marrow microenvironment where tumor cells are well protected and nurtured by stromal and other accessory cells. Ibrutinib inhibited the adhesion of AML cells to bone-marrow stromal cells (BMSCs) in the co-culture system at the potency required to inhibit BTK activity (Rushworth 2014). Interaction between AML cells and the bone marrow microenvironment is believed to be critical in regulating tumor survival and resistance to chemotherapy. In fact, inhibition of AML blast adhesion to BMSCs has been associated with improved tumor cytotoxicity (Becker 2012).

The effect of BTK inhibition on tumor microenvironment via ibrutinib has been investigated in various types of blood cancer, namely CLL, MCL and multiple myeloma. For example, ibrutinib significantly reduced adhesion and migration of MCL cells in co-culture with BMSCs. In human MCL patients, treatment with ibrutinib resulted in transient mobilization of lymphocytes or light chain-restricted CD19+CD5+ cell fraction into the peripheral blood with concomitant decrease of tumor volume. These results suggested that ibrutinib alone promoted tumor cell egress from the microenvironment and sensitized them to cell death (Chang 2013a).

In summary, ibrutinib appears to have a dual anti-AML effect through 1) potentially mobilizing cells from its protective microenvironment and 2) exhibiting direct anti-proliferative/cytotoxic activity. These preclinical studies provided a strong rationale for investigation of ibrutinib against AML as a single agent or a cell-mobilizing/chemo-sensitizing agent in combination with other chemotherapeutics such as cytarabine or hypomethylating agents.

2. STUDY OBJECTIVES

2.1. Primary Objectives

- To evaluate the efficacy of ibrutinib monotherapy or in combination with either LD-AraC or azacitidine in the treatment of Acute Myeloid Leukemia (AML) using the overall remission rate (defined as proportion of subjects achieving a CR or CRi) according to the LeukemiaNet guidelines (Döhner 2010).

- To evaluate the safety and tolerability of ibrutinib monotherapy or in combination with either LD-AraC or azacitidine in subjects with AML

2.2. Secondary Objectives

- To evaluate clinical efficacy by assessing relapse-free survival (RFS), event-free survival (EFS) and overall survival (OS)
- To evaluate clinical benefit defined as CR, CRi, morphologic leukemia-free state, and partial remission (PR)

2.3. Exploratory Objectives

- To determine the pharmacokinetics (PK) of ibrutinib monotherapy or in combination with either LD-AraC or azacitidine in an AML population
- To evaluate prognostic and predictive biomarkers relative to treatment outcomes (ie, Btk/pBtk, secreted proteins, gene expression profiling, mutational analysis)

3. STUDY DESIGN

3.1. Overview of Study Design

This Phase 2a open-label, non-randomized, U.S. multicenter study is designed to evaluate the safety and efficacy of ibrutinib monotherapy or in combination with either cytarabine or azacitidne in the treatment of subjects with AML.

A maximum of 101 response evaluable subjects will be enrolled in up to 3 treatment cohorts:

- Cohort 1 – ibrutinib monotherapy: ibrutinib 560 mg once daily on a continuous basis.
- Cohort 2 – ibrutinib + LD-AraC: ibrutinib 560 mg once daily on a continuous basis plus low dose cytarabine.
- Cohort 3 – ibrutinib + azacitidine: ibrutinib 560 mg once daily on a continuous basis plus IV azacitidine.

The study will begin with a safety run-in in the ibrutinib + LD-AraC combination cohort only. Six subjects will receive ibrutinib at a dose level of 560 mg once daily on a continuing basis starting 2 days prior to the first cytarabine dose. LD-AraC will be administered at 20 mg twice daily (BID) subcutaneously (sc) for 10 days of a 28-day cycle.

During the initial safety run-in, the 6 subjects will be assessed for dose limiting toxicities (DLTs) during the first treatment cycle. The DLT assessment period may be extended for up to 2 weeks beyond the end of the first cycle for pancytopenia follow up without treatment interruption. (Refer to Section 5.2 for details).

If 2 of the 6 subjects experience DLT(s) (Section 5.2), 3 additional subjects will be assessed for DLTs. If 3 or more of the 9 subjects experience DLTs, enrollment will be halted at the 560 mg

dose level. At Sponsor's discretion a dose of 420 mg ibrutinib or lower (plus LD-AraC) may be explored.

If less than 2 out of 6 subjects or less than 3 out of 9 subjects experience DLT(s), additional subjects will be enrolled in one of two treatment cohorts:

- Cohort 1 – ibrutinib monotherapy: up to 33 response evaluable subjects will receive ibrutinib 560 mg once daily on a continuous basis

  OR
- Cohort 2 – ibrutinib + LD-AraC: up to 25-28 additional response evaluable subjects (for a total of 34) will receive ibrutinib 560 mg once daily (or a lower dose) on a continuous basis starting 2 days prior to first cytarabine dose (20 mg BID sc) for 10 days of a 28-day cycle

Subjects will be assigned to either treatment cohort at the discretion of the treating investigator.

Efficacy parameters will be monitored closely. In the event response assessments suggest futility in the ibrutinib + AraC cohort, further enrollment in both the ibrutinib monotherapy and the ibrutinib + AraC cohorts will be closed and a new cohort (Cohort 3) of ibrutinib + azacitidine will be started:

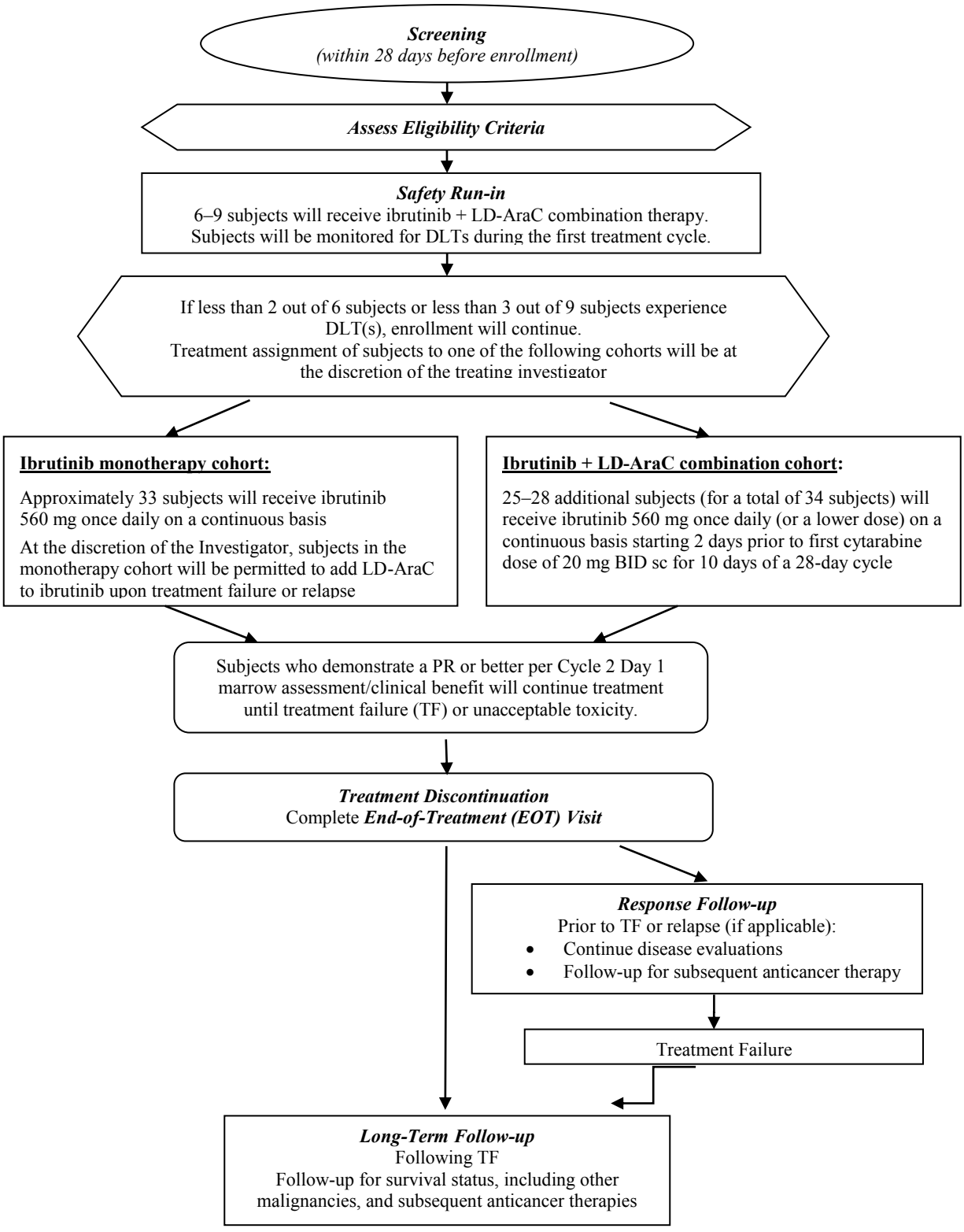
- Cohort 3 – ibrutinib + azacitidine: up to 34 response evaluable subjects will receive ibrutinib 560 mg once daily on a continuous basis starting 1 day prior to first azacitidine dose + azacitidine 75 mg/m^2 IV once daily on Days 1-7 of a 28-day cycle (with an option to increase to 100 mg/m^2 after 2 cycles).

For Cohort 3, the same safety run-in principle (6+3 design) will be implemented. If less than 2 out of 6 subjects or less than 3 out of 9 subjects experience DLT(s), additional subjects will be enrolled. If 3 or more of the 9 subjects experience DLTs, enrollment will be halted at the 560 mg dose level. At Sponsor's discretion a dose of 420 mg ibrutinib or lower (plus azacitidine) may be explored.

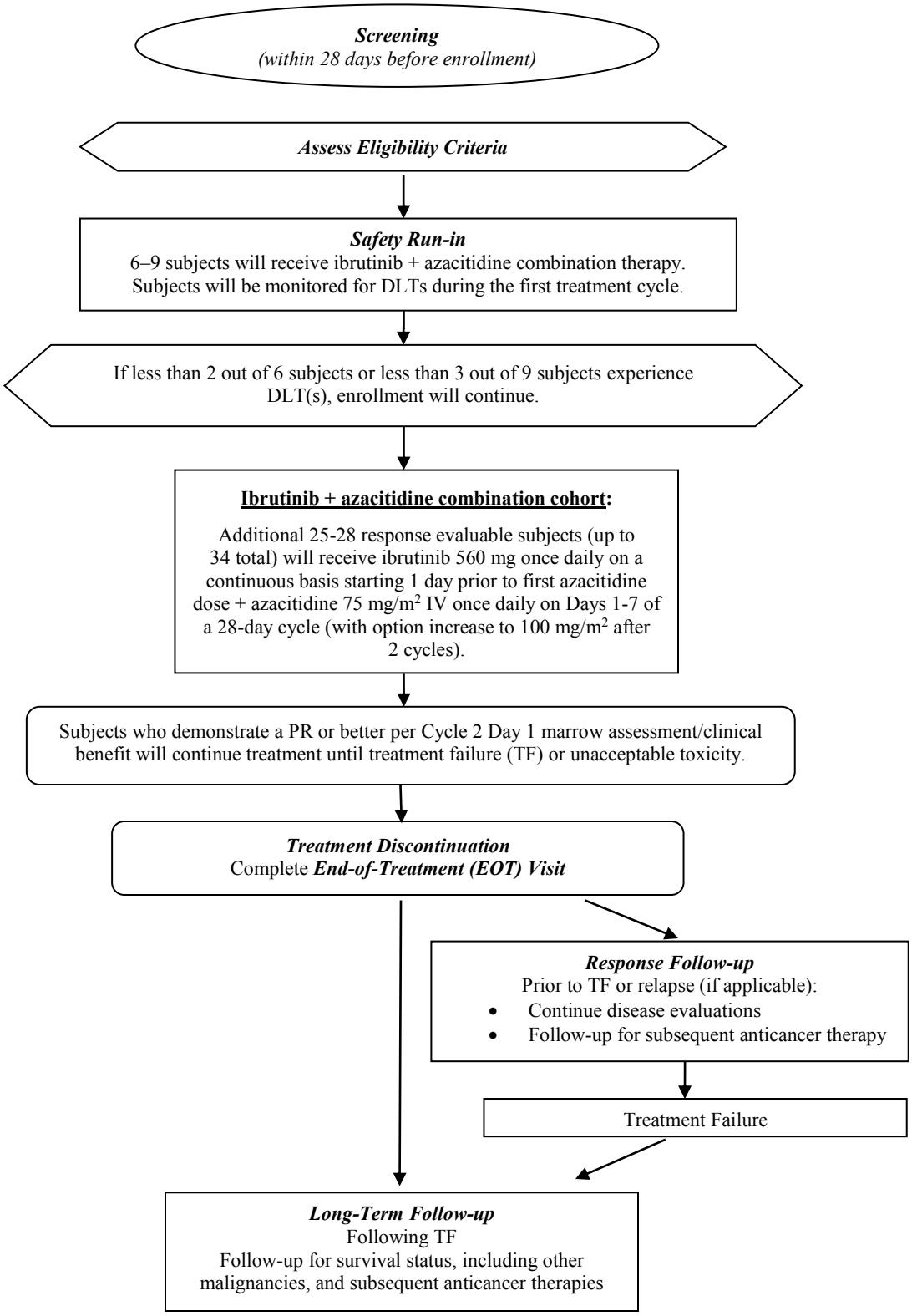
Study treatment will continue in subjects who demonstrate a PR or better on their Cycle 2 Day 1 bone marrow assessment according to the LeukemiaNet guidelines (Döhner 2010), or based on clinical benefit as determined by the treating physician. Treatment may continue thereafter until unacceptable toxicity, treatment failure (TF), or withdrawal of consent.

Subjects treated in the ibrutinib monotherapy cohort who experience a documented TF or relapse will be permitted to add the protocol-specified dose and regimen of LD-AraC to ibrutinib per investigator discretion, and will follow the combination cohort schedule and procedures (Appendix 1) beginning with the Cycle 1 Day 1 visit. Baseline parameters for response will be based on the most recent bone marrow and hematology results prior to the first dose of add-on LD-AraC.

3.1.1. Study Schema – Cohorts 1 and 2



3.1.2. Study Schema – Cohorts 3



3.2. Study Design Rationale

This is a Phase 2a study designed to assess the safety and efficacy of ibrutinib as monotherapy or in combination with either LD-AraC or azacitidine in treatment naïve or relapsed/refractory subjects with AML.

Ibrutinib alone or in combination with other treatments has demonstrated a favorable safety profile in CLL and non-Hodgkin lymphoma. The addition of ibrutinib to LD-AraC or to azacitidine in this study may improve the outcomes of thesetreatments for AML, and ibrutinib monotherapy may constitute an alternative for subjects with AML who cannot tolerate or refuse standard treatment options.

Ibrutinib will be added to the LD-AraC or the azacitidine standard regimens recommended for elderly or unfit AML subjects. Based on the enhanced cytotoxic effect of ibrutinib and chemotherapy in AML cell lines (Rushworth 2014), it is hypothesized that the addition of ibrutinib will improve treatment outcomes with limited effect on tolerability. Ibrutinib inhibits blast proliferation of human AML cells and BTK was shown to be constitutively phosphorylated in the majority of AML cells evaluated (Rushworth 2014), providing a rationale for the clinical evaluation of ibrutinib in AML patients. These data suggest that BTK inhibition may result in therapeutic response in AML, either directly and/or by enhancing the effects of conventional chemotherapy in AML.

Initially, the safety of the ibrutinib + LD-AraC combination will be assessed in 6–9 subjects. If less than 2 out of 6 subjects or less than 3 out of 9 subjects experience DLT(s) during the first treatment cycle, enrollment will continue in the ibrutinib monotherapy and the ibrutinib +LD-AraC cohorts as described in Section 3.1. Subjects who experience TF or relapse on ibrutinib monotherapy will have an opportunity, at the discretion of the investigator, to be treated with add-on LD-AraC in combination with ibrutinib.

Efficacy parameters will be monitored closely. In the event response assessments suggest futility in the ibrutinib + AraC cohort, further enrollment in both the ibrutinib monotherapy and the ibrutinib + AraC cohorts will be closed and a new cohort of ibrutinib + azacitidine will be started using the same safety run-in principle (6+3 design).

3.2.1. Study Population and Treatment

The study will enroll adult subjects with pathologically documented AML that have failed standard treatment, or subjects without prior therapy who refuse standard chemotherapy.

Ibrutinib monotherapy or in combination with either LD-AraC or azacitidine will be investigated. The assigned study treatment will continue in subjects who at the time of their Cycle 2 Day 1 bone marrow assessment, demonstrate at least a PR according to the LeukemiaNet guidelines (Döhner 2010), or clinical benefit as determined by the treating physician. Treatment

may continue thereafter until unacceptable toxicity, treatment failure, withdrawal of consent, or any other reason for discontinuation of treatment as named in Section 9.2.

At the discretion of the Investigator, subjects in the ibrutinib monotherapy cohort will be permitted to add LD-AraC upon designation of treatment failure or relapse.

3.2.2 Dose Selection

The selected dose of ibrutinib is 560 mg (4 x 140 mg capsules) once daily. Although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours postdose at dose levels ≥2.5 mg/kg. Average dose-normalized ibrutinib exposure, based on AUC, was approximately 2 times higher in the 2.5 mg/kg dose cohort in the PCYC-04753 study. Given the atypically high level of exposure to ibrutinib at the 2.5 mg/kg dose level and the inter patient variability in plasma levels observed in this study (coefficient of variation [CV] for C_{max} = 59% to 136% and CV for AUC = 60% to 107%), there was concern that in a larger population some patients may experience low exposures and may not achieve the targeted pharmacodynamic effect. Therefore, a dose greater than 2.5 mg/kg was considered necessary to achieve consistent, full BTK occupancy. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration. This dose has shown to be safe in Phase 1 and Phase 2 studies conducted in various B-cell malignancies alone and in combination with other agents.

4. SUBJECT SELECTION

4.1. Inclusion Criteria

To be enrolled in the study, each potential subject must satisfy all of the following inclusion criteria.

Disease Related

1. Pathologically documented AML that has failed standard treatment (based on NCCN guidelines), or subjects without prior therapy who refuse standard treatment options.
2. Screening bone marrow aspirate/biopsy results showing >5% blasts.
3. White blood cell (WBC) count <25,000 cells/mm^3 (25 x 10^9/L).
   - The use of hydroxyurea (HU) during the screening phase is permitted to control the peripheral blood count until 1 day (~5 half lives) prior study treatment.
4. Platelet count >10,000 cells/mm^3 (10 x $10^{9/}$L).
5. Adequate hepatic and renal function defined as:

- For Cohorts 1 and 2: serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤3.0 x upper limit of normal (ULN); for Cohort 3: ALT ≤2.5 or AST ≤2.5 ULN.
- Serum creatinine ≤2 mg/dL or Estimated Creatinine Clearance ≥30 mL/min (Cockcroft-Gault).
- Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin).

6. PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). When treated with warfarin or other vitamin K antagonists, then INR ≤3.0).

Demographic

7. Male and female ≥18 years of age.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.

Ethical/Other

9. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of reproductive potential must have a negative serum pregnancy test upon study entry.
10. Male and female subjects of reproductive potential agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[1], or sterilized partner) during the period of therapy and for 90 days after the last dose of study drug.

4.2. Exclusion Criteria

To be enrolled in the study, potential subjects must meet NONE of the following exclusion criteria:

Disease-Related

1. Acute promyelocytic leukemia (French-American-British Class M3 AML).
2. Known active central nervous system (CNS) leukemia.
3. Known active systemic infection (Grade ≥2).
4. Active bleeding disorders or clinical signs of bleeding (Grade ≥2).
5. Prior bone marrow transplant that requires immunosuppressant therapy or presents with graft vs host disease (GVHD).

[1] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Concurrent Conditions

6. History of other malignancies, except:
   - Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study drug and with low risk of recurrence by treating physician.
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
   - Adequately treated carcinoma in situ without evidence of disease.
7. Prior treatment with a BTK inhibitor.
8. For Cohort 3 subjects, prior treatment with hypomethylating agents (eg, azacitidine, decitabine)
9. Anticancer therapy including chemotherapy, immunotherapy, radiotherapy, hormonal or any investigational therapy within 14 days or 5 half-lives (whichever is shorter) prior to first dose of study drug.
10. Subject has received a monoclonal antibody for anticancer intent within 8 weeks prior to the first dose of study drug.
11. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
12. Recent infection requiring intravenous (IV) systemic treatment that was completed ≤14 days before the first dose of study drug.
13. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4.03), Grade 0 or 1, unless otherwise defined in the inclusion/exclusion criteria with the exception of alopecia.
14. Known bleeding disorders (eg, von Willebrand's disease) or hemophilia.
15. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
16. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
17. Major surgery within 4 weeks of first dose of study drug.
18. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
19. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
20. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.

21. Concomitant use of warfarin or other Vitamin K antagonists.
22. Requires treatment or prophylaxis with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix 5).
23. Currently active, clinically significant hepatic impairment (≥ moderate hepatic impairment according to the Child Pugh classification [Appendix 7]).
24. Lactating or pregnant.
25. Unwilling or unable to participate in all required study evaluations and procedures.
26. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).

5. TREATMENT OF SUBJECTS

5.1. Treatment Allocation and Blinding

There will be no blinded study treatments. This is an open-label, non-randomized study. The first 6–9 subjects will be allocated to the ibrutinib + LD-AraC combination cohort. If less than 2 out of 6 subjects or less than 3 out of 9 of the subjects experience DLTs during the first treatment cycle, additional subjects will be enrolled in two treatment cohorts: ibrutinib monotherapy or ibrutinib + LD-AraC.

Treatment assignment to either cohort will be at the discretion of the treating investigator until enrollment targets for each cohort are met. In the event efficacy assessments suggest futility in the ibrutinib + LD-AraC cohort, further enrollment in both the ibrutinib monotherapy and the ibrutinib + LD-AraC cohorts will be closed and a new cohort of ibrutinib + azacitidine will be started using the same safety run-in principle (6+3 design) described above.

5.2. Definition of Dose Limiting Toxicity (DLT)

The first 6 subjects will be assessed for DLTs. DLTs will be assessed during the first treatment cycle. However, prolonged pancytopenia in the presence of a hypocellular bone marrow that lasts ≥6 weeks (42 days) from the start of therapy will be considered a DLT (see below).

Hematologic:

Due to the nature of this disease, hematologic AEs will not be considered DLTs.

- However, prolonged pancytopenia in the presence of a hypocellular bone marrow (ie, cellularity 5% or less without evidence of leukemia) that lasts ≥6 weeks (42 days) from the start of therapy will be considered dose limiting myelosuppression.

Non-Hematologic:

- Any Grade ≥3 non-hematologic event (NCI CTCAE, v4.03) that occurs during the first treatment cycle (C1D1 – C2D1pre-dose) and is considered-related to the study treatment in the opinion of the investigator with the following modifications:
  - Grade 3 nausea, vomiting or diarrhea persisting ≤7 days
  - Grade 3 fatigue persisting ≤7 days
  - Grade 3 infection is not a DLT, however an infection with life-threatening consequences or requiring urgent intervention (Grade 4) will be considered a DLT

If 2 or more of the 6 subjects experience DLT(s) during the assessment period, 3 additional subjects will be assessed for DLTs. If 3 or more of the 9 subjects experience DLTs, enrollment will be halted at the 560 mg dose level. At Sponsor's discretion a dose of 420 mg ibrutinib or lower (plus LD-AraC) may be explored.

If less than 2 out of 6 subjects or less than 3 out of 9 subjects experience DLT(s), additional subjects will be enrolled.

Replacement of subjects:

If a subject misses ≥7 of the 30 planned ibrutinib doses and/or: for Cohort 2, ≥5 of the 20 planned LD-AraC doses; for Cohort 3, ≥2 of the 7 planned azacitidine doses, from the first ibrutinib dose (Run-in Day 1) to Cycle 1 Day 28 for reasons other than toxicity (eg, non-compliance), or if a subject ends treatment for any reason other than toxicity, (eg, withdraws consent, treatment failure), the subject will be replaced. This replacement rule will apply only to the safety run-in subjects.

5.3. Study Treatment

Cohort 1 –ibrutinib monotherapy: ibrutinib 560 mg once daily on a continuous basis

Cohort 2 –ibrutinib + LD-AraC: ibrutinib 560 mg once daily on a continuous basis and LD-AraC 20 mg BID sc for 10 days of a 28-day cycle. This cohort will receive ibrutinib alone for 2 days prior to the start of the LD-AraC regimen.

Cohort 3 – ibrutinib + azacitidine: ibrutinib 560 mg once daily on a continuous basis and azacitidine 75 mg/m^2 IV once daily on Days 1-7 of a 28-day cycle. This cohort will receive ibrutinib alone for 1 day prior to starting azacitidine. At the investigator's discretion, the azacitidine dose may be increased to 100 mg/m^2 after 2 cycles.

5.4. Study Medication

5.4.1. Ibrutinib

5.4.1.1. Formulation/Packaging/Storage

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib IB for a list of excipients.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drugs will be dispensed in child-resistant packaging.

Refer to the Pharmacy Manual for additional guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.4.1.2. Dose and Administration

Ibrutinib 560 mg (4 x 140 mg capsules) is administered orally once daily. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix 5).

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

The first dose will be delivered in the clinic, after which subsequent dosing is typically on an outpatient basis, except for days on which PK samples are to be drawn in the clinic. On the PK sampling days, the subject will be required to hold that day's ibrutinib dose so that the dose can be administered by the study staff who will record the exact time of dose. Ibrutinib will be dispensed to subjects in bottles. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records (Section 12.8) updated at each visit. Returned capsules must not be redispensed to anyone.

5.4.1.3. Overdose

Any dose of study drug administered in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

There is no specific experience in the management of ibrutinib overdose in patients. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 11.4 for further information regarding AE reporting.

5.4.1.4. Dose Modification for Adverse Reactions

Due to the nature of this disease, hematologic AEs will not be considered DLTs except in the case of prolonged myelosuppression, defined as marrow cellularity of <5% without evidence of leukemia on Day 42 or later (6 weeks) from start of therapy. During the first 6 weeks, *platelets should be maintained at a minimum level of 10,000/µL per institutional guidelines.*

The dose of ibrutinib should be modified according to the dose modification guidance in Table 1 if any of the following toxicities occur:

- Grade 4 neutropenia ANC (<500/µL) for more than 7 days (not applicable during the first 42 days of study treatment). Not applicable during the first 42 days of study treatment.
- The use of neutrophil growth factors is permitted per institutional policy after the first treatment cycle and must be recorded in the electronic case report form (eCRF).
- Grade 4 thrombocytopenia (platelets<25,000/µL). Not applicable during the first 42 days of study treatment.
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy.
- Any other Grade 4 or unmanageable Grade 3 toxicity attributed to study drug.
- For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anti-coagulants or anti-platelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.2.4).

In the event that the investigator feels that a necessary dose modification other than the recommendations above is required, please consult the medical monitor to discuss for approval.

If the dose of ibrutinib is reduced, at the investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the Dose Administration eCRF.

Table 1. Ibrutinib Dose Modifications

Occurrence	Action to be Taken
First	Withhold ibrutinib until recovery of AEs to Grade ≤1 or baseline, may restart at original dose level
Second	Withhold ibrutinib until recovery of AEs to Grade ≤1 or baseline, may restart at 1 dose level lower (ie, 280 mg/day for 420 mg/day dose; 420 mg/day for 560 mg/day dose)
Third	Withhold ibrutinib until recovery of AEs to Grade ≤1 or baseline, may restart at 1 dose level lower (ie, 140 mg/day for 420 mg/day dose; 280 mg/day for 560 mg/day dose)
Fourth	Discontinue ibrutinib

Dose modifications must be recorded in the Dose Administration eCRF.

For required dose modification for hepatic impairment refer to Section 5.4.1.5 and for concomitant treatment with CYP3A inhibitors refer to Section 6.2.1.

Study treatment should be discontinued in the event of a toxicity lasting more than 28 days, unless reviewed and approved by the medical monitor.

5.4.1.5. Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child- Pugh class B or C) are excluded from study participation. For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib/placebo is to a level of 280 mg daily (two capsules). For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (Refer to Appendix 7).

5.4.2. LD-AraC

5.4.2.1. Formulation/Packaging/Storage

Cytarabine for sc injection will be supplied by the investigative site.

5.4.2.2. Dose and Administration

Low-dose cytarabine (LD-AraC) will be administered at 20 mg BID subcutaneously (sc) for 10 days of a 28-day cycle.

5.4.2.3. Overdose

Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

5.4.2.4. Dose Modification for Adverse Reactions

Toxicities should be managed per institutional practice. Dosing with LD-AraC may resume at the same dose upon recovery. Missed doses will not be replaced and treatment cycles will not be prolonged.

5.4.3. Azacitidine

5.4.3.1. Formulation/Packaging/Storage

Azacitidine for IV infusion will be supplied by the investigative site.

5.4.3.2. Dose and Administration

Azacitidine will be administered at 75 mg/m^2 IV once daily on Days 1-7 of a 28-day cycle. Subjects should be premedicated for nausea and vomiting. At the investigator's discretion, the azacitidine dose may be increased to 100 mg/m^2 IV once daily on Days 1-7 of a 28-day cycle after 2 cycles.

5.4.3.3. Overdose

Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

5.4.3.4. Dose Modification for Adverse Reactions

Toxicities should be managed per institutional practice. Missed doses will not be replaced.

5.5. Criteria for Permanent Discontinuation of Study Drug

Investigators are encouraged to keep a subject who is experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. For a complete list of criteria for permanent discontinuation of study treatment, refer to Section 9.2.

A Follow-up Visit (Section 8.4) is required for all subjects except for those subjects who have withdrawn full consent (see Section 9.3).

6. CONCOMITANT MEDICATIONS/PROCEDURES

Concomitant therapies must be recorded from the time of ICF signing until 30 days after the last dose of study drug.

6.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Transfusions may be given in accordance with institutional policy.

Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy after the first treatment cycle and in accordance with the ASCO guidelines (Smith 2006) after completion of Cycle 1.

After consultation with the medical monitor the following may be considered; localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted.

Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100 mg per day of prednisone or equivalent.

The use of hydroxyurea (HU) during the screening phase is permitted to control the peripheral blood count until 1 day (~5 half lives) prior study treatment.

6.2. Medications to be Used with Caution

6.2.1. CYP3A Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Subjects taking prophylactic antifungals that are moderate CYP3A inhibitors prior to starting dosing with ibrutinib may continue receiving the antifungals and will start ibrutinib at 140 mg daily.

- If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, or cobicistat) must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, or dronedarone) must be used, reduce

ibrutinib to 140 mg for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Section 5.4.1.2).

- No dose adjustment is required in combination with mild inhibitors.

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

For subjects who must start a moderate or strong CYP3A inhibitor while on treatment with ibrutinib, additional PK blood samples for evaluation of ibrutinib exposure will be requested (see Section 7.1.3.4).

A list of common CYP3A inhibitors and inducers is provided in Appendix 5. For further information, please refer to the current version of the IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

6.2.2. Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor. Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available. Therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin, should be taken at least 6 hours before or after ibrutinib.

6.2.3. QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic electrocardiogram (ECG) and electrolyte monitoring should be considered.

6.2.4. Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied.For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries see Section 6.4.

Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation) consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

6.3. Prohibited Concomitant Medications

Any non-study protocol related chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving ibrutinib treatment.

Corticosteroids for the treatment of the underlying malignancy are prohibited. Refer to Section 6.1 for further guidance.*Erythropoietic growth factors (eg, erythropoietin) and neutrophil growth factors (eg, filgrastim and peg-filgrastim) are prohibited during the first treatment cycle during the DLT assessment period.*

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.4. Guidelines for Ibrutinib Management with Surgeries or Procedures

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

6.4.1. Minor Surgical Procedures

For minor procedures (such as a central line placement, needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib.

6.4.2. Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

6.4.3. Emergency Procedures

For emergency procedures, ibrutinib should be held as soon as possible and until the surgical site is reasonably healed or for at least 7 days after the urgent surgical procedure, whichever is longer.

7. STUDY EVALUATIONS

7.1. Description of Procedures

A cycle has a duration of 28 days throughout this study.

All screening clinical and laboratory assessments must be performed within 28 days of Study Day 1 and prior to the first dose of study treatment.

All study tests and procedures should be performed at the study center at which the subject was enrolled and will be receiving treatment with the exception of specified lab specimens designated to be shipped to a central lab or PCYC for analysis.

7.1.1. Assessments

7.1.1.1. ICF

The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved informed consent form (ICF) confirming his or her willingness to participate in this study before any study-specific screening procedures are performed.

Subjects must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA). In addition, subjects must sign all approved ICF amendments per the site IRB/REB/IEC guidelines during the course of the study.

The subject may be enrolled in the study only after signing the ICF and being deemed eligible for entry based on screening procedures and history review.

7.1.1.2. Confirm Eligibility

All necessary screening procedures and evaluations, along with review of medical history, must be performed to document that the subject meets all of the inclusion criteria and none of the exclusion criteria and prior to first dose on Day 1 (Section 4). In addition to the review of screening procedures and results, documentation of pathologic confirmation of disease (AML) is required for confirmation of eligibility prior to enrollment.

Each subject must have an Eligibility Checklist completed by the site and review/approved by the Sponsor medical monitor prior to enrollment.

7.1.1.3. Medical History and Demographics

The subject's relevant medical history through review of medical records and by interview will be collected and recorded. Concurrent medical signs and symptoms during screening and prior to first dose of study treatment must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and a list of all prior anticancer treatments, dates administered, response, and duration of response to these treatments is required to be clearly documented in the subject's medical records.

7.1.1.4. Prior and Concomitant Medications

All medications from the signing of ICF through 30 days after the last dose of study drug will be documented. After a subject discontinues study treatment, receipt of all subsequent anticancer therapies will be collected until one of the following events takes place: death, subject withdrawal of full consent, subject is deemed lost to follow-up, or the study is terminated by Sponsor.

7.1.1.5. Adverse Events

The accepted regulatory definition for an adverse event (AE) is provided in Section 11.1. The occurrence of AE at the time the ICF is signed until first dose should be recorded under medical history in the eCRF form. All medical occurrences after the first dose with study drug until 30 days after the last dose of study drug that meet the AE definition must be recorded as AEs in the eCRF. Laboratory abnormalities deemed clinically significant by the Investigator will also be documented as AEs.

Additional important requirements for AE and SAE reporting are explained in Section 11.4.

7.1.1.6. Physical Examination

The Screening and End-of-Treatment physical examination will include, at a minimum, the general appearance of the subject, height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system. This complete physical examination will also be required at the Day 1 visit for each study Cycle as well as the TF and End-of-Treatment visits. Periodically monitor subjects clinically for atrial fibrillation.

A limited symptom-directed physical examination is required weekly during the first 2 study cycles, unless a complete physical examination is required as above.

7.1.1.7. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature and will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

7.1.1.8. ECOG

This assessment must be performed during the screening assessments as well as the day of the first study treatment and prior to the first dose. Subsequent assessments will be performed as per the Schedule of Assessments (Appendix 1, Appendix 2, and Appendix 3).

The ECOG performance index is provided in Appendix 4. A score of 2 or less is required for enrollment.

7.1.2. Laboratory

7.1.2.1. Hematology

Hematology parameters will include a complete blood count including platelets and differential.

Subjects with platelet counts ≤25,000/µL at baseline or during the first cycle will be required to have platelet assessment 3 times a week until the end of first treatment cycle. Thereafter, follow the Schedule of Assessment and hematological and dosing guidelines provided in Section 5.4.1.4).

7.1.2.2. Chemistry (Serum)

Serum chemistry parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN)/Urea, creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, uric acid, magnesium and bicarbonate.

7.1.2.3. Coagulation Studies

Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at Screening using a local laboratory.

7.1.2.4. Hepatitis Serologies

Hepatitis serologies include Hepatitis C antibody, Hepatitis B surface antigen, , and Hepatitis B core antibody and will be evaluated. If Hepatitis B core antibody, Hepatitis B surface antigen, or Hepatitis C antibody is positive, then PCR to quantitate Hepatitis B DNA or hepatitis C RNA must be performed and must be negative prior to enrollment.

7.1.2.5. Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

7.1.2.6. Pregnancy Test

Serum or urine pregnancy test will be required at Screening by local laboratory only for women of childbearing potential. A serum or urine pregnancy test will also be performed on Day 1 prior to first dose. If positive, pregnancy must be ruled out by ultrasound to be eligible. This test may be performed more frequently if required by local regulatory authorities.

7.1.3. Diagnostics/Procedures

7.1.3.1. ECG

ECGs should be performed at screening and subsequently at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea.

During visits in which both ECGs and blood draws are performed, ECGs should be performed first.

At Screening, 12-lead ECG will be done in triplicate (≥1 minute apart); the calculated QTcF average of the 3 ECGs must be <470 msec for eligibility.

Abnormalities noted at Screening should be included in the medical history.

7.1.3.2. Bone Marrow Aspirate/Biopsy

A bone marrow aspirate/biopsy will be obtained at screening within 7 days before the first dose of ibrutinib, at Cycle 2 Day 1 (±3 days), Cycle 4 Day 1 (±3 days), then every 3 cycles (±5 days) (ie, Cycles 7, 10, and 13), and every 6 cycles (±5 days) thereafter until designation of TF or withdrawal of consent.

Subjects with prolonged pancytopenia (≥42 days) and hypocellular bone marrow (ie, cellularity 5% or less without evidence of leukemia) at the Cycle 2 Day 1 assessments must undergo an additional bone marrow assessment on Day 42 (±3 days) after initiation of study treatment.

At each time point, up to an additional 10 unstained slides and up to 20 mL aspirate samples will be collected for biomarker evaluation. These blood and bone marrow aspirate samples will be used to help identify genes and other markers that may enhance our understanding of the cancer and/or determine how subjects respond (positively or negatively) to ibrutinib.

Refer to the Laboratory Manual for detailed collection and handling procedures for the additional aspirate samples and slides noted above.

7.1.3.3. Cytogenetics/Karyotype

Cytogenetic and karyotype assessments will be performed on the screening bone marrow sample and may be performed on additional bone marrow samples collected during the study.

7.1.3.4. Cerebrospinal Fluid Collection

In subjects who develop CNS progression, cerebrospinal fluid (CSF) will be obtained for PK, PD, and other disease related testing. At the time of CSF sampling, one additional blood PK sample would be required.

Refer to the Laboratory Manual for detailed collection and handling procedures.

7.1.3.5. Pharmacokinetics

Plasma concentrations of ibrutinib and PCI-45227 will be determined using a validated analytical method. Other potential metabolites of ibrutinib may be explored. Refer to the Schedule of Assessments (Appendix 1, Appendix 2, and Appendix 3) and the Pharmacokinetic Sample Schedule (Table 2, Table 3, and Table 4).

Table 2. Ibrutinib + LD-AraC Combination Cohort

Period	Study Day	Predose	Time After Dosing[a]			
			1h±15 min	2 h±15 min	4 h±30 min	6 h±1 h
Ibrutinib Run-in	1	X	X	X	X	X
Ibrutinib Run-in	2	X[b]				
Cycle 1	8	X	X	X	X	X

[a] Record actual time of sample collection.
[b] Sample collected 24 hours (±2 hours) after Day 1 dose and prior to dosing on Day 2.

Table 3. Ibrutinib Monotherapy Cohort

Period	Study Day	Predose	Time After Dosing[a]			
			1h±15 min	2 h±15 min	4 h±30 min	6 h±1 h
Cycle 1	1	X	X	X	X	X
	2	X[b]				
	8	X	X	X	X	X

[a] Record actual time of sample collection.
[b] Sample collected 24 hours (±2 hours) after Day 1 dose and prior to dosing on Day 2.

Table 4. Ibrutinib + Azacitidine Combination Cohort

Period	Study Day	Predose	Time After Dosing[a]			
			1h±15 min	2 h±15 min	4 h±30 min	6 h±1 h
Ibrutinib Run-in	1	X	X	X	X	X
Cycle 1	1	X[b]		X		
Cycle 1	7	X	X	X	X	X

[a] Record actual time of sample collection.
[b] Sample collected 24 hours (±2 hours) after Run-in Day 1 dose and prior to dosing with ibrutinib and azacitidine on Cycle 1 Day 1.

Pharmacokinetic Sample Collection for Subjects Starting a Concomitant CYP3A Inhibitor While on Ibrutinib Treatment

For subjects who must start a moderate or strong CYP3A inhibitor while on treatment with ibrutinib, additional PK blood samples for evaluation of ibrutinib exposure is requested at the following scheduled visit after concomitant CYP3A inhibitor has started and is still in use. PK samples will be collected at the following timepoints:

- Pre-dose (If possible, sample should be obtained 22–24 hours post the previous day's dose and before dosing on the day of the scheduled visit)
- 1 hour ± 15 min
- 2 hours ± 15 min
- 4 hours ± 30 min
- 6 hours ± 1 h

Refer to the Laboratory Manual for instructions on collecting and processing these samples. On the day of the sampling visit, the clinical staff will instruct the subject to not take a dose before arrival at the clinic. Study drug intake will be observed by clinic staff. The actual time (versus requested time) that each sample is drawn must be recorded using a 24 hour format. The same clock should be used for recording the time of dosing.

7.1.3.6. T/B/NK Cell Count

The blood sample(s) for T/B/NK cell count ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16/56^+$) must be collected before dosing at the protocol specified timepoints. Percentages and absolute counts of $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD56^+$ and $CD16/56^+$ cells will be determined. Reference the Schedule of Assessments (Appendix 1, Appendix 2, and Appendix 3) for other sample timepoints for this assay.

7.1.3.7. Predictive Biomarkers and Mechanisms of Resistance

Identification of signaling pathways or biomarkers that predict sensitivity or resistance to ibrutinib will be explored in this study.

A predose blood sample will be collected as shown in the schedule of events. Samples collected may be used for pharmacodynamic and biomarker assessments including BTK and other kinase activity and signaling, expression analysis, sequencing, flow cytometry and secreted protein analyses.

A portion of pre-treatment bone marrow samples collected may be used by Sponsor for further biomarker analysis.

7.1.3.8. Genetic and Molecular Prognostic Markers

Cytokines, chemokines, cell surface markers and exploratory investigations of predictive biomarkers and mechanism of resistance will be tested in peripheral blood and bone marrow. Samples will be collected from all subjects. Bone marrow aspirate will be collected at the time points specified in the Schedule of Assessment (Appendix 1, Appendix 2, and Appendix 3).

Samples may be tested to evaluate potential biomarkers related to disease response and investigate potential mechanism of treatment resistance. These samples may be characterized by technologies such as gene expression profiling, targeted sequencing for genomic alterations and intracellular pathway analysis. Inhibition of BTK and other related kinases may also be explored. These efforts may identify biomarkers that could assist with future development of this compound. Pharmacodynamics assays, ie, BTK occupancy, may be performed to correlate results of biomarker assessments to the physiological effects of ibrutinib.

7.2. Efficacy Evaluations

A bone marrow aspirate/biopsy will be obtained at screening within 7 days before the first dose of ibrutinib. Follow up bone marrow examination for efficacy evaluation will be performed at Cycle 2 Day 1 (±3 days), at Cycle 4 Day 1 (±3 days), then every 3 cycles on Day 1 (±5 days) of Cycles 7, 10, 13, and every 6 cycles (±5 days) thereafter until designation of TF or withdraw of consent. Peripheral blood and bone marrow aspirate smears will be examined morphologically for changes in AML blast counts using routine diagnostic procedures at the investigative site. Determination of response will be made by the Investigator according to the LeukemiaNet guidelines (Döhner 2010).

Complete Remission (CR)

Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 x 10^9/L (1000/µL); platelet count >100 x 10^9/L (100,000/µL); independence of red cell transfusions (all criteria need to be fulfilled).

Complete Remission with Incomplete Recovery (CRi)

All CR criteria except for residual neutropenia (<1.0 x 10^9/L [1000/µL]) or thrombocytopenia (<100 x 10^9/L [100000/µL]).

Morphologic Leukemia-Free State

Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required.

Partial Remission (PR)

All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%.

Treatment Failure (TF)

Failure to achieve at least a PR; relapse from CR or CRi, or death from any cause.

Relapse

Bone marrow blasts >5%; or reappearance of blasts in the blood; or development of extramedullary disease.

Investigator will be permitted to add the protocol-specified LD-AraC regimen for subjects treated in the ibrutinib monotherapy cohort who experience a documented treatment-failure (TF) or relapse. These subjects will follow the combination cohort schedule and procedures (Appendix 1) beginning with the Cycle 1 Day 1 visit. Baseline parameters for response will be based on the most recent bone marrow and hematology results prior to the first dose of add-on LD-AraC.

7.3. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in source documents for transcription to the eCRF or laboratory requisition form. Refer to the Schedule of Assessments (Appendix 1, Appendix 2, and Appendix 3) for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the Laboratory Manual.

8. STUDY PROCEDURES

8.1. Overview

For each subject enrolled, this study is divided into a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Schedules of Assessments (Appendix 1, Appendix 2, and Appendix 3) summarize the frequency and timing of efficacy, PK, biomarker, and safety measurements and procedures that are applicable to this study.

8.2. Screening Phase

Screening procedures will be performed up to 28 days prior to the first dose of study treatment, unless otherwise specified. Obtain written informed consent as indicated by subject's signature on the IRB/IEC approved ICF.

- Informed Consent
- Medical history and demographics
- Complete physical exam including height and weight
- ECOG Performance Status
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- 12-lead ECG (in triplicate [≥1 minute apart])
- Review and recording of all current, ongoing medications and any medications taken within 30 days prior to start of study medication (including over-the-counter drugs, vitamins and herbs)
- Bone marrow aspirate and biopsy including bone marrow smear slides (within 7 days before the first administration of study drug)
- Laboratory tests for:
  - Hematology including differential
  - Serum chemistry
  - Coagulation (PT/INR and PTT)
  - Serum pregnancy test (for women of childbearing potential only)
  - Hepatitis serologies: Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B surface antibody, and Hepatitis B core antibody
  - Urinalysis
- Review of eligibility criteria
- Confirm eligibility – complete enrollment checklist and submit to Sponsor for review/approval prior to enrollment
- Assignment to treatment cohort

8.3. Treatment Phase

Following completion of the Screening Visit and once eligibility has been confirmed, subjects are enrolled. Enrollment should occur as close to the time of the expected first dose as possible, ie, not more than 3 business days prior to expected first dose with study drug.

8.3.1. Treatment Visits - Ibrutinib + LD-AraC Combination Cohort

8.3.1.1. Ibrutinib Run-in Day 1 Visit

Predose

- Review of medical history and demographics
- Review of current medications and any new medications since screening visit
- Review of current signs/symptoms including any new untoward events since screening
- Complete physical exam and weight
- Vital signs
- ECOG status

- Reconfirm eligibility
- Laboratory tests for:
  - Hematology including differential
  - Serum chemistry
- Laboratory blood samples for:
  - PK analysis
  - T/B/NK
  - Biomarkers (blood)

Postdose

- Dose administration – ibrutinib
- Provide drug diary and dosing instructions to subject
- Dispense study drug to subject for run-in and Cycle 1
- PK blood sample collection at
  - 1 hour (±15 min)
  - 2 hours (±15 min)
  - 4 hours (±30 min)
  - 6 hours (±1 hour)
- Biomarker blood sample at 4 hours (±30 min)

8.3.1.2. Ibrutinib Run-in Day 2 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- PK blood sample collection

Postdose

- Dose administration - ibrutinib

8.3.1.3. Cycle 1 Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Vital signs
- Lab sample collection for
  - Hematology including differential (Subjects with platelet counts ≤25,000/μL will be required to have platelet assessment 3 times a week until the end of first treatment cycle)
  - Serum chemistry
  - Biomarkers (blood)

Postdose

- Dose administration – LD-AraC
- Dose administration – ibrutinib
- Dispense study drugs

8.3.1.4. Cycle 1 Day 8 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Vital signs
- Symptom directed physical exam
- Laboratory sample collection for:
  - Hematology including differential (Subjects with platelet counts ≤25,000/μL will be required to have platelet assessment 3 times a week until the end of first treatment cycle)
  - Serum chemistry
  - PK analysis

Postdose

- Dose administration – LD-AraC
- Dose administration – ibrutinib
- PK blood sample collection
  - 1 hour (±15 min)
  - 2 hours (±15 min)
  - 4 hours (±30 min)
  - 6 hours (±1 hour)

8.3.1.5. Cycle 1 Day 15 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Vital signs
- Symptom directed physical exam
- ECOG status
- Lab sample collection for

- Hematology including differential (Subjects with platelet counts ≤25,000/µL will be required to have platelet assessment 3 times a week until the end of first treatment cycle)
- Serum chemistry
- Biomarkers (blood)

Postdose

- Dose administration – ibrutinib

8.3.1.6. Cycle 1 Day 22 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Vital signs
- Symptom directed physical exam
- Lab sample collection for
  - Hematology including differential (Subjects with platelet counts ≤25,000/µL will be required to have platelet assessment 3 times a week until the end of first treatment cycle)
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.1.7. Cycle 2 Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Complete physical exam
- Vital signs
- ECOG status
- Bone marrow aspiration and biopsy including bone marrow smear slides
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - T/B/NK cell count
  - Biomarkers (blood)

Postdose

- Dose administration – ibrutinib
- Dose administration – LD-AraC
- Provide drug diary and dosing instructions to subject
- Dispense study drugs

8.3.1.8. Cycle 2 Day 8 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Symptom directed physical exam
- Vital signs
- Lab sample collection for
  - Hematology
  - Serum chemistry

Postdose

- Dose administration – ibrutinib
- Dose administration – LD-AraC

8.3.1.9. Cycle 2 Day 15 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Symptom directed physical exam
- Vital signs
- ECOG status
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.1.10. Cycle 2 Day 22 Visit

Predose

- Review of concomitant medications

- Review of adverse events
- Review returned subject dosing diary
- Symptom directed physical exam
- Vital signs
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.1.11. Cycle 3 Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Complete physical exam
- Vital signs
- ECOG status
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - T/B/NK cell count
  - Biomarkers (blood)

Postdose

- Dose administration – ibrutinib
- Dose administration – LD-AraC
- Provide drug diary and dosing instructions to subject
- Dispense study drugs

8.3.1.12. Cycle 3 Day 15 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.1.13. Cycle 4 Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Complete physical exam
- Vital signs
- ECOG status
- Bone marrow aspirate and biopsy including bone marrow smear slides
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - T/B/NK cell count
  - Biomarkers(blood)

Postdose

- Dose administration – ibrutinib
- Dose administration – LD-AraC
- Provide drug diary and dosing instructions to subject
- Dispense study drugs

8.3.1.14. Cycle 4 Day 15 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.1.15. Cycle 5 and Beyond, Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Complete physical exam
- Vital signs
- ECOG status
- Bone marrow aspirate and biopsy including bone marrow smear slides (Cycles 7, 10, 13, then every 6 cycles thereafter)
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - Biomarkers (blood)

Postdose

- Dose administration – ibrutinib
- Dose administration – LD-AraC
- Provide drug diary and dosing instructions to subject
- Dispense study drugs

8.3.2. Treatment Visits - Ibrutinib Monotherapy Cohort

8.3.2.1. Cycle 1 Day 1 Visit

Predose

- Review of medical history and demographics
- Review of concomitant medications
- Review of adverse events
- Complete physical exam
- Vital signs
- ECOG status
- Reconfirm eligibility
- Lab sample collection for:
  - Hematology including differential (Subjects with platelet counts ≤25,000/μL will be required to have platelet assessment 3 times a week until the end of first treatment cycle)
  - Serum chemistry
  - T/B/NK Cell count
  - Biomarkers (blood)

- PK analysis

Postdose

- Dose administration – ibrutinib
- Provide drug diary and dosing instructions to subject
- Dispense study drug to subject for at-home dosing
- PK blood sample collection analysis at
  - 1 hour (±15 min)
  - 2 hours (±15 min)
  - 4 hours (±30 min)
  - 6 hours (±1 hour)

8.3.2.2. Cycle 1 Day 2 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Symptom directed physical exam
- Vital signs
- Lab sample collection for:
  - Hematology including differential (Subjects with platelet counts ≤25,000/µL will be required to have platelet assessment 3 times a week until the end of first treatment cycle)
  - Serum chemistry
  - PK analysis (Day 2 predose or 24 hours post Day 1 dose)

Postdose

- Dose administration – ibrutinib

8.3.2.3. Cycle 1, Day 8 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Vital signs
- Symptom directed physical exam
- Lab sample collection for
  - Hematology including differential (Subjects with platelet counts ≤25,000/µL will be required to have platelet assessment 3 times a week until the end of first treatment cycle)

- Serum chemistry
- PK blood sample collection

Postdose

- Dose administration – ibrutinib
- Post-dose PK blood sample collection at:
  - 1 hour (±15 min)
  - 2 hours (±15 min)
  - 4 hours (±30 min)
  - 6 hours (±1 hour)

8.3.2.4. Cycle 1 Day 15 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Vital signs
- Symptom directed physical exam
- ECOG status
- Lab sample collection for
  - Hematology including differential (Subjects with platelet counts ≤25,000/µL will be required to have platelet assessment 3 times a week until the end of first treatment cycle)
  - Serum chemistry
  - Biomarkers (blood)

Postdose

- Dose administration – ibrutinib

8.3.2.5. Cycle 1 Day 22 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Vital signs
- Symptom directed physical exam
- Lab sample collection for
  - Hematology including differential (Subjects with platelet counts ≤25,000/µL will be required to have platelet assessment 3 times a week until the end of first treatment cycle)

- Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.2.6. Cycle 2 Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Complete physical exam
- Vital signs
- ECOG status
- Bone marrow aspiration and biopsy including bone marrow smear slides
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - T/B/NK cell count
  - Biomarkers (blood)

Postdose

- Dose administration – ibrutinib
- Provide drug diary and dosing instructions to subject
- Dispense study drug to subject for at-home dosing

8.3.2.7. Cycle 2 Day 8 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Symptom directed physical exam
- Vital signs
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.2.8. Cycle 2 Day 15 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Symptom directed physical exam
- Vital signs
- ECOG status
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.2.9. Cycle 2 Day 22 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Symptom directed physical Exam
- Vital signs
- ECOG status
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.2.10. Cycle 3 Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Complete physical exam
- Vital signs
- ECOG status

- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - T/B/NK cell count
  - Biomarkers (blood)

Postdose

- Dose administration – ibrutinib
- Provide drug diary and dosing instructions to subject
- Dispense study drug to subject for at-home dosing

8.3.2.11. Cycle 3 Day 15 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.2.12. Cycle 4 Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Complete physical exam
- Vital signs
- ECOG status
- Bone marrow aspirate and biopsy including bone marrow smear slides
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - T/B/NK cell count
  - Biomarkers (blood)

Postdose

- Dose administration – ibrutinib

- Provide drug diary and dosing instructions to subject
- Dispense study drug to subject for at-home dosing

8.3.2.13. Cycle 4 Day 15 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.2.14. Cycle 5 and Beyond, Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Complete physical exam
- Vital signs
- ECOG status
- Bone marrow aspirate and biopsy including bone marrow smear slides (Cycles 7, 10, 13, then every 6 cycles thereafter)
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - Biomarkers (blood)

Postdose

- Dose administration – ibrutinib
- Provide drug diary and dosing instructions to subject
- Dispense study drug to subject for at-home dosing

8.3.3. Treatment Visits - Ibrutinib + Azacitidine Combination Cohort

8.3.3.1. Ibrutinib Run-in Day 1 Visit

Predose

- Review of medical history and demographics
- Review of current medications and any new medications since screening visit
- Review of current signs/symptoms including any new untoward events since screening
- Complete physical exam and weight
- Vital signs
- ECOG status
- Reconfirm eligibility
- Laboratory tests for:
  - Hematology including differential
  - Serum chemistry
- Laboratory blood samples for:
  - PK analysis
  - T/B/NK
  - Biomarkers (blood)

Postdose

- Dose administration – ibrutinib
- Provide drug diary and dosing instructions to subject
- Dispense study drug to subject for run-in and Cycle 1
- PK blood sample collection at
  - 1 hour (±15 min)
  - 2 hours (±15 min)
  - 4 hours (±30 min)
  - 6 hours (±1 hour)
- Biomarker blood sample at 4 hours (±30 min)

8.3.3.2. Cycle 1 Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Vital signs
- Lab sample collection for
  - Hematology including differential (Subjects with platelet counts ≤25,000/μL will be required to have platelet assessment 3 times a week until the end of first treatment cycle)

- Serum chemistry
- Biomarkers (blood)
- PK analysis

Postdose

- Dose administration – azacitidine
- Dose administration – ibrutinib
- Dispense study drugs
- PK blood sample collection at
  - 2 hours (±15 min)

8.3.3.3. Cycle 1 Day 7 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Vital signs
- Symptom directed physical exam
- Laboratory sample collection for:
  - Hematology including differential (Subjects with platelet counts ≤25,000/μL will be required to have platelet assessment 3 times a week until the end of first treatment cycle)
  - Serum chemistry
  - PK analysis

Postdose

- Dose administration – ibrutinib
- Dose administration – azacitidine
- PK blood sample collection
  - 1 hour (±15 min)
  - 2 hours (±15 min)
  - 4 hours (±30 min)
  - 6 hours (±1 hour)

8.3.3.4. Cycle 1 Day 15 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Vital signs

- Symptom directed physical exam
- ECOG status
- Lab sample collection for
  - Hematology including differential (Subjects with platelet counts ≤25,000/μL will be required to have platelet assessment 3 times a week until the end of first treatment cycle)
  - Serum chemistry
  - Biomarkers (blood)

Postdose

- Dose administration – ibrutinib

8.3.3.5. Cycle 1 Day 22 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Vital signs
- Symptom directed physical exam
- Lab sample collection for
  - Hematology including differential (Subjects with platelet counts ≤25,000/μL will be required to have platelet assessment 3 times a week until the end of first treatment cycle)
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.3.6. Cycle 2 Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Complete physical exam
- Vital signs
- ECOG status
- Bone marrow aspiration and biopsy including bone marrow smear slides
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - T/B/NK cell count

- Biomarkers (blood)

Postdose

- Dose administration – ibrutinib
- Dose administration – azacitidine
- Provide drug diary and dosing instructions to subject
- Dispense study drugs

8.3.3.7. Cycle 2 Day 7 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Symptom directed physical exam
- Vital signs
- Lab sample collection for
  - Hematology
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.3.8. Cycle 2 Day 15 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Symptom directed physical exam
- Vital signs
- ECOG status
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.3.9. Cycle 2 Day 22 Visit

Predose

- Review of concomitant medications

- Review of adverse events
- Review returned subject dosing diary
- Symptom directed physical exam
- Vital signs
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.3.10. Cycle 3 Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Complete physical exam
- Vital signs
- ECOG status
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - T/B/NK cell count
  - Biomarkers (blood)

Postdose

- Dose administration – ibrutinib
- Dose administration – azacitidine
- Provide drug diary and dosing instructions to subject
- Dispense study drugs

8.3.3.11. Cycle 3 Day 15 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.3.12. Cycle 4 Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Complete physical exam
- Vital signs
- ECOG status
- Bone marrow aspirate and biopsy including bone marrow smear slides
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - T/B/NK cell count
  - Biomarkers(blood)

Postdose

- Dose administration – ibrutinib
- Dose administration – azacitidine
- Provide drug diary and dosing instructions to subject
- Dispense study drugs

8.3.3.13. Cycle 4 Day 15 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

Postdose

- Dose administration – ibrutinib

8.3.3.14. Cycle 5 and Beyond, Day 1 Visit

Predose

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Complete physical exam
- Vital signs
- ECOG status
- Bone marrow aspirate and biopsy including bone marrow smear slides (Cycles 7, 10, 13, then every 6 cycles thereafter)
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - Biomarkers (blood)

Postdose

- Dose administration – ibrutinib
- Dose administration – azacitidine
- Provide drug diary and dosing instructions to subject
- Dispense study drugs

8.3.4. Treatment Failure (TF) Visit

- Review of concomitant medications
- Review of adverse events
- Complete physical exam
- Vital signs
- ECOG status
- Bone marrow aspirate and biopsy including bone marrow smear slides
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - Collection of CSF if CNS involvement is suspected
  - T/B/NK
  - Biomarkers (blood)
  - PK sample (blood) upon collection of CSF

8.3.5. End-of-Treatment (EOT) Visit

An EOT visit should occur 30 days (±7 days) from the last dose of study drug or prior to the start of a new anticancer treatment. If a subject starts a new anticancer treatment less than 7 days after

the TF visit, only those procedures not conducted at the TF should be performed at the EOT visit.

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Complete physical exam
- Vital signs
- ECOG status
- ECG
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry
  - Coagulation (PT, INR, aPTT)
  - Urinalysis
  - T/B/NK
  - Biomarkers (blood)

8.4. Follow-up Phase

Once a subject has completed the End-of-Treatment Visit they will enter the Follow-up Phase. Subjects who withdraw from treatment for reasons other than TF will participate in ongoing response follow-up.

8.4.1. Response Follow-up (RFU)

The response follow-up period will begin when the subject withdraws for any reason other than TF, until the subject experiences a TF or starts an alternative anticancer therapy. During this period, subject will return to the clinic approximately every 3 months (±14 days) and the following procedures should be performed.

- ECOG performance status
- Bone marrow aspirate and biopsy including bone marrow smear slides (per investigator discretion)
- Lab sample collection for
  - Hematology including differential
  - Biomarkers (blood)
- Subsequent anticancer therapy

8.4.2. Long-Term Follow-up (LTFU)

Once subjects experience TF, relapse, or start use of alternative anticancer therapy (for subjects who have not withdrawn consent), they will be contacted approximately every 3 months

(±14 days) by clinic visit or telephone until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first.

- Survival status, including other malignancies
- Subsequent anticancer therapy

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost to follow up, or has not withdrawn consent before the end of study.

9.2. Withdrawal from Study Treatment

Study treatment will be discontinued in the event of any of the following events:

- Treatment failure or no evidence of clinical benefit per investigator assessment
- Unacceptable toxicity: an intercurrent illness or adverse event that prevents further ibrutinib administration.
- Withdrawal of consent for treatment by subject
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
- Study termination by Sponsor
- Subject becomes pregnant

All subjects, regardless of reason for discontinuation of study treatment will undergo an End of Treatment Visit and be followed for treatment failure and survival.

The Investigator should notify the Sponsor within 24 hours if a subject discontinues ibrutinib treatment due to treatment failure. These subjects should stay in the study to be followed for survival.

9.3. Withdrawal from Study

Withdrawal from study (including all follow-up) will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the subject
- Lost to follow-up
- Study termination by Sponsor
- Death

If a subject is lost to follow-up, every reasonable effort should be made by the study site personnel to contact the subject. The measures taken to follow up should be documented.

When a subject withdraws before completing the study, the following information should be documented in the source documents:

- Reason for withdrawal;
- Whether the subject withdraws full consent (ie, withdraws consent to treatment and all further contact) or partial consent (ie, withdraws consent to treatment but agrees to participate in follow-up visits)

10. STATISTICAL METHODS AND ANALYSIS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

10.1. Demographics, Baseline Characteristics and Study Conduct

Subject demographics (including age, sex, and race/ethnicity) and other baseline characteristics (including ECOG performance status, disease burden, and number of prior therapies) will be summarized. Summary statistics will include means, standard deviations, and medians for continuous variables and proportions for categorical variables.

10.2. Endpoints

10.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the overall remission rate (ORR). The ORR is defined as the proportion of subjects who achieve either a complete remission (CR) or complete remission with incomplete blood recovery (CRi) as best response as assessed by the investigator according to the LeukemiaNet guidelines (Döhner 2010). ORR will be calculated for the response evaluable population for each cohort separately.

Response evaluable subjects are defined as subjects who had at least 1 post-baseline response assessment or any subjects who died due to an AML-related cause or were discontinued early due to an AML-related event without at least 1 post-baseline response assessment.

10.2.2. Secondary Efficacy Endpoints

The efficacy of 3 treatment cohorts (ibrutinib monotherapy, ibrutinib with LD-AraC, and ibrutinib with azacitidine) will be evaluated separately for relapse-free survival (RFS), event-free survival (EFS), overall survival (OS), and clinical benefit rate (CBR).

For subjects achieving CR or CRi, relapse-free survival (RFS) will be calculated to determine durability. RFS will be measured from the date criteria for remission are met (CR or CRi), whichever is recorded first, until the date of death or the earliest date of relapse is objectively documented.

EFS will be obtained for the response evaluable population. EFS will be measured from the date of first dose to the date of treatment failure (failure to achieve at least a PR), relapse from CR or CRi, or death from any cause, whichever occurs first.

For EFS and RFS, subjects who start subsequent anticancer therapy, who are event free and alive at the time of clinical cut-off, or who have unknown status will be censored at the date of the last disease assessment prior the start of subsequent therapy or the clinical cut-off time. Subjects with no post-baseline disease assessment will be censored on the date of Day 1.

OS will be measured from the time of first study drug administration until the date of death from any cause. Data for subjects who have not died will be censored at the date of the last known contact. The estimates will be calculated using the all treated population.

Clinical benefit rate (CBR) defined as the proportion of subjects who achieve CR, CRi, morphologic leukemia-free state, or PR as best response as assessed by the investigator. CBR will be calculated for the response evaluable population for each cohort.

10.3. Sample Size Determination

The sample size of 6 or 9 subjects for safety review was based on clinical experience and conventional DLT studies.

The sample size was calculated to detect a meaningful signal of clinical activity of each treatment cohort while minimizing risk of continuing enrollment under null conditions. The sample size was estimated for each treatment cohort without multiplicity adjustment.

The sample size of 33 subjects was calculated to test the null hypothesis that the ORR of ibrutinib monotherapy is ≤5% (not clinically compelling) versus the alternative hypothesis that ORR will be ≥20%, with a significance level of 5%, and 80% power.

The sample size of 34 subjects was calculated to test the null hypothesis that the ORR of ibrutinib plus LD-AraC or azacitidine is ≤15% (not clinically compelling) versus the alternative hypothesis that ORR will be ≥35%, with a significance level of 5%, and 80% power.

10.4. Efficacy Analysis

The primary efficacy endpoint is the ORR for each of each treatment cohort as defined by to the LeukemiaNet guidelines (Döhner 2010). The point estimate of the rate and the corresponding exact binomial 95% confidence interval will be calculated individually for each treatment cohort on response evaluable population.

The secondary efficacy endpoints, RFS, EFS, and OS, will be calculated using the Kaplan-Meier procedure for each cohort.

For CBR, the point estimate of the rate and the corresponding exact binomial 95% confidence interval will be calculated individually for the 3 treatment cohorts.

10.5. Safety Analysis

Analysis of safety data will be conducted on the all treated population, which includes enrolled subjects who receive at least 1 dose of ibrutinib. The baseline value for safety assessments will be defined as the last value on or before the day of the first dose of study drugs if we do not specify. The safety analyses will be based on the monitoring of adverse events, survival status, ECOG performance status, vital signs measurements, and clinical laboratory results.

The safety variables to be analyzed include adverse events, clinical laboratory test results (hematology and chemistry), physical examination findings, and vital signs measurements. Exposure to ibrutinib first dose and reasons for discontinuation from study treatment will be tabulated. In general, continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation and range). Categorical variables will be summarized using frequencies and percentages. No formal statistical testing is planned.

Adverse Events

Adverse event parameters to be evaluated are the type, incidence, and intensity of adverse events; the relationship of adverse events to ibrutinib; and the action taken with respect to ibrutinib treatment due to adverse events.

The verbatim terms used in the eCRF by Investigators to identify non-hematological adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are those adverse events (including worsening of an existing event) occurring after the first dose of study drugs and within 30 days following the last dose of study drug or the first date starting new anticancer therapy, whichever is earliest; any adverse event that is considered study drug-related regardless of the start date of the event.
All treatment-emergent adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. The number and percent of subjects with treatment-emergent adverse events will be summarized according to intensity (NCI CTCAE, v4.03) and drug relationship as well as categorized by system organ class and preferred term. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory tests will be summarized separately for hematology and serum chemistry. Local laboratory results will be standardized using the International System SI unit. Selected hematologic and chemistry laboratory parameters are detailed in Section 7.1.2.1. All laboratory

values will be graded using the NCI CTCAE v4.03. The worst toxicity grade during the study will be tabulated.

Descriptive statistics will be provided for the values of selected clinical laboratory tests at each scheduled on-treatment evaluation including the final value. Percent change from baseline to each scheduled on-treatment evaluation and to the final value will also be summarized. For selected variables, the mean value and mean percent change over time will be presented graphically.

A summary of the shifts in selected laboratory hematology and serum chemistry parameters from baseline to the worst toxicity grade during the study will be provided. The worst toxicity grade during the study will be tabulated.

10.6. Pharmacokinetic Analysis

Bioanalytical data from this study will be used in noncompartmental PK analysis and also may be combined with data from other studies performed with ibrutinib in subjects with hematologic malignancies as part of a population PK analysis using nonlinear mixed effects models. For the population PK analysis, covariates that could potentially correlate with plasma PK parameters will be evaluated. The results of the population PK analyses (if performed) will be presented in a separate report.

Plasma concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Descriptive statistics will be used to summarize ibrutinib and PCI-45227 concentrations at each sampling time point and PK parameters of ibrutinib and PCI-45227: including but not limited to C_{max}, T_{max}, AUC_{last}, and $t_{1/2}$.

Mean plasma ibrutinib and PCI-45227 concentration time profiles will be plotted.

10.7. Biomarker Analyses

- Changes in peripheral T/B/NK count and profiling of immunophenotypes
- BTK active site percent occupancy in peripheral blood cells
- Changes in secreted protein levels (ie, chemokines, cytokines)
- Identification of cytogenetic abnormalities, tumor mutations and other biomarkers associated with sensitivity or resistance to ibrutinib

Clinically relevant biomarkers may be associated with clinical responses. Changes in biomarkers over time will be summarized by treatment cohort. Association between baseline levels and changes from baseline in select markers and response to treatment will be explored.

11. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

11.1. Definitions

11.1.1. Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (ICH-E2A, 1995).

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term “disease progression” should not be reported as an adverse event term but instead symptoms/clinical signs of disease progression may be reported.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the subject and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the subject through the completion of final study procedures.
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE.

Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.

- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

11.1.2. Serious Adverse Events

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death (ie, the AE actually causes or leads to death).
- Is life-threatening. Life-threatening is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the Investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.
- Requires inpatient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

Given that the Investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the Sponsor or the Investigator believes that the event is serious, the event will be considered serious.

11.1.3. Severity Criteria (Grade 1-5)

Definitions found in the CTCAE v4.03 will be used for grading the severity (intensity) of nonhematologic AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities

- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

11.1.4. Causality (Attribution)

The Investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Related:	The AE is clearly related to use of the investigational product.

11.2. Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the Investigator's Brochure/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

11.3. Special Reporting Situations

Special reporting situation on a Sponsor study may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of any study drug
- Suspected abuse/misuse of a study drug
- Inadvertent or accidental exposure to a study drug
- Medication error involving a product (with or without subject/subject exposure to the study drug, eg, name confusion)

Occurrence of any special reporting situations should be recorded in the eCRF. If any special reporting situation meets the criteria of an adverse event, it should be recorded on the adverse events eCRF. If the adverse event is considered serious, it should be recorded on the adverse events eCRF as serious and should be reported on the Serious Adverse Event Report Form. The SAE Report Form should be sent via email or fax to Pharmacyclics Drug Safety or designee within 24 hours of awareness.

11.4. Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

11.4.1. Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation timepoints during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded in the subject's medical record and on the Adverse Event CRF and, when applicable, on the Serious Adverse Event Report Form.

Each recorded adverse event or serious adverse event will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

11.4.2. Adverse Event Reporting Period

All AEs whether serious or non-serious, will be documented in the source documents from the time signed and dated ICF is obtained until 30 days following the last dose of study drug. SAEs will be reported to the Sponsor from the time of ICF signing. Both serious and non-serious AEs will be recorded in the eCRF from the first dose of study drug until 30 days after the last dose of study drug.

Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be

provided.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported. (See Section 11.1.1)

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. Autopsy, postmortem reports and death certificates must be forwarded to the Sponsor, or designee, as outlined above, if allowed per local regulatory guidelines.

If a death occurs within 30 days after the last dose of study drug, the death must be reported to the Sponsor as a serious adverse event.

11.4.3. Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events (initial and follow-up information) will be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of the discovery of the event or information. Pharmacyclics may request follow-up and other additional information from the Investigator (eg, hospital admission/discharge notes and laboratory results). The contact information (phone, email and fax) for Pharmacyclics Drug Safety can be found on the Serious Adverse Event Report Form and instructions.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities and governing bodies according to the local regulations.

The investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

11.4.4. Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 30 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 3 months (90 days) after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

11.4.5. Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including follow-up for overall survival.

11.4.6. Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) should be

reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of awareness.

11.4.6.1. Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic AEs of Grade 3 or higher*. Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as Grade 3 or higher AE per CTCAE v4.03.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.4.6 above.

12. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

12.1. Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with applicable local regulations (including US Code of Federal Regulations [CFR] Title 21 and European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

12.2. Institutional Review Board (IRB), Research Ethics Board (REB) and Independent Ethics Committee (IEC) Approval

The Investigator will submit this protocol, the ICF, IB, and any other relevant supporting information (eg, all advertising materials or materials given to the subject during the study) to the appropriate IRB/REB/IEC for review and approval before study initiation. Amendments to the protocol and informed consent form must also be approved by the IRB/REB/IEC before the implementation of changes in this study.

The Investigator is responsible for providing the IRB/REB/IEC with any required information before or during the study, such as SAE expedited reports or study progress reports.

The IRB/REB/IEC must comply with current United States (US) regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

The following documents must be provided to Pharmacyclics or its authorized representative before entering subjects in this study: (1) a copy of the IRB/REB/IEC letter that grants formal approval; and (2) a copy of the IRB/REB/IEC-approved ICF.

12.3. Informed Consent

The ICF and process must comply with the US regulations (§ 21 CFR Part 50) as well as country specific national regulations and/or local laws. The ICF will document the study-specific information the Investigator or his/her designee provides to the subject and the subject's agreement to participate.

The Investigator or designee (designee must be listed on the Delegation of Authority log), must explain in terms understandable to the subject the purpose and nature of the study, study procedures, anticipated benefits, potential risks, possible AEs, and any discomfort participation in the study may entail. This process must be documented in the subject's source record. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed. The original and any amended signed and dated consent forms must remain in each subject's study file at the study site and be available for verification by study monitors at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

12.4. Quality Control and Quality Assurance

Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

12.5. Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to Section 12.3), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The Investigator or designee must explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Pharmacyclics and its designees, regulatory agencies, and IRBs/REBs/IECs. As the study Sponsor, Pharmacyclics will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the Investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the subject and to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations.

12.6. Study Files and Record Retention

The Investigator must keep a record that lists all subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, the reason(s) for exclusion is to be recorded.

The Investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments, IRB/REB/IEC approval letters (dated), signed Form FDA 1572 and Financial Disclosures, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed (electronically), dated and completed CRFs, and documentation of CRF corrections, SAE forms transmitted to Pharmacyclics and notification of SAEs and related reports, source documentation, normal laboratory values, decoding procedures for blinded studies, curricula vitae for study staff, and all relevant correspondence and other documents pertaining to the conduct of the study.

All essential documentation will be retained by the Investigator for at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The Investigator must notify Pharmacyclics and obtain written approval from Pharmacyclics before destroying any clinical study documents or images (eg, scan, radiograph, ECG tracing) at any time. Should an Investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to Pharmacyclics. Pharmacyclics will inform the Investigator of the date that study records may be destroyed or returned to Pharmacyclics.

Pharmacyclics must be notified in advance of, and Pharmacyclics must provide express written approval of, any change in the maintenance of the foregoing documents if the Investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the Investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the Investigator and Pharmacyclics to store such documents in sealed containers away from the study site so that they can be returned sealed to the Investigator for audit purposes.

12.7. Case Report Forms and Record Maintenance

CRFs will be used to collect the clinical study data and must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (ie, listed on the Delegation of Authority log) will complete CRFs designed for this study according to the completion guidelines that will be provided. The Investigator will ensure that the CRFs are accurate, complete, legible, and completed within a reasonable period of time. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data.

The CRFs exists within an electronic data capture (EDC) system with controlled access managed by Pharmacyclics or its authorized representative for this study. Study staff will be appropriately trained in the use of CRFs and application of electronic signatures before the start of the study and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The Investigator attests that the information contained in the CRFs is true by providing electronic signature within the EDC system. After database lock, the Investigator will receive a copy of the subject data (eg, paper, CD, or other appropriate media) for archiving at the study site.

12.8. Investigational Study Drug Accountability

Ibrutinib and any comparator used must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the Investigator or other site personnel supply ibrutinib or comparator to other Investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Pharmacyclics.

Accountability records for ibrutinib and any comparator must be maintained and readily available for inspection by representatives of Pharmacyclics and are open to inspections by regulatory authorities at any time.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. Study identification number (PCYC-1131-CA)
2. Subject identification number
3. Lot number(s) of ibrutinib or comparator dispensed for that subject
4. Date and quantity of drug dispensed
5. Any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Pharmacyclics' requirements. If the site cannot meet Pharmacyclics' requirements for disposal/destruction, arrangements will be made between the site and Pharmacyclics or its representative, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

12.9. Study Monitoring/Audit Requirements

Representatives of Pharmacyclics or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the Investigator and site staff, remote monitoring, as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions and regulatory guidelines, and to ensure the quality and integrity of the data. This study is also subject to reviews or audits.

To assure the accuracy of data collected in the CRFs, it is mandatory that the monitor/auditor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the Investigator agrees to allow the IRB/REB/IEC, representatives of Pharmacyclics, its designated agents and authorized employees of the appropriate Regulatory Authority to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

Pharmacyclics or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. In the event of such an inspection, Pharmacyclics will be available to assist in the preparation. All pertinent study data should be made available as requested to the Regulatory Authority for verification, audit, or inspection purposes.

12.10. Investigator Responsibilities

A complete list of Investigator responsibilities are outlined in the clinical trial research agreement and the Statement of Investigator Form FDA 1572, both of which are signed by the Investigator before commencement of the study. In summary, the Investigator will conduct the

study according to the current protocol; will read and understand the IB; will obtain IRB/REB/IEC approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB/REB/IEC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB/ REB/IEC according to the specifics outlined in this protocol; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

12.11. Sponsor Responsibilities

A complete list of the Sponsor responsibilities is outlined in the clinical trial research agreement and in the laws and regulation of the country in which the research is conducted. In summary, the Sponsor will select qualified Investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, conduct the study in accordance with the general investigational plan and protocols and promptly inform Investigators, health and regulatory agencies/authorities as appropriate of significant new adverse effects or risks with respect to the drug.

12.12. Financial Disclosure

A separate financial agreement will be made between each Principal Investigator and Pharmacyclics or its authorized representative before the study drug is delivered.

For this study, each Investigator and Subinvestigator (as designated on the Form FDA1572) will provide a personally signed Financial Disclosure Form in accordance with § 21 CFR 54. Each Investigator will notify Pharmacyclics or its authorized representative of any relevant changes in financial disclosure information during the conduct of the study and for 1 year after the study has been completed.

12.13. Liability and Clinical Trial Insurance

In the event of a side effect or injury, appropriate medical care as determined by the Investigator/designee will be provided.

The ICF will include a description treatment in the event of a study related injury and handling of the costs associated therewith, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

12.14. Protocol Amendments

Pharmacyclics will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/REB/IEC together with, if applicable, a revised model ICF. Written documentation of IRB/REB/IEC and required site approval must be received by Pharmacyclics before the amendment may take effect at each site. Additionally under this circumstance, information on any change in risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand and sign each revised ICF confirming willingness to remain in the trial.

No other significant or consistent change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the Investigator and Pharmacyclics.

12.15. Publication of Study Results

Pharmacyclics may use the results of this clinical study in registration documents for Regulatory Authorities in the US or abroad. The results may also be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an Investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Pharmacyclics reserves the right to preview all manuscripts and abstracts related to this study, allowing Pharmacyclics sufficient time to make appropriate comments before submission for publication.

In most cases, the Investigators at the sites with the highest accruals of eligible subjects shall be listed as lead authors on manuscripts and reports of study results. The medical monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Pharmacyclics and in accordance with current standards for authorship as recorded in professional conference and journal submission instructions.

12.16. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor and the Investigator will arrange discontinuation procedures. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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14. APPENDICES

Appendix 1: Schedule of Assessments – Ibrutinib + LD-AraC Combination Cohort

Study Cycle		Ibrutinib Run-in		C1				C2				C3		C4		C5 & Beyond	TF	EOT[a]	RFU[b]	LTFU
Study Day		1	2	1	8	15	22	1	8	15	22	1	15	1	15	1				
								(±2 days)				(±2 days)		(±2 days)		(±2 days)	**Any time**	(±7d)	(±14 days)	
Study Drug Administration																				
Ibrutinib (continuous)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
LD-AraC (for 10 days every 4 wks)				Days 1-10				Days 1-10				Days 1-10		Days 1-10		Days 1-10				
Procedure	**Screening** Day -28 to -1																			
Informed consent	X																			
Medical history & demographics	X	X																		
Review Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Review adverse events[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Complete Physical Exam & Weight[e]	X	X						X				X		X		X	X	X		
Symptom directed physical exam					X	X	X		X	X	X									
Vital signs[f]	X	X		X	X	X	X	X	X	X	X	X		X		X	X	X		
ECOG performance status	X	X				X		X		X		X		X		X	X	X	X	
Triplicate 12-Lead ECG[g]	X	If clinically indicated (eg, subjects with palpitations, lightheadedness)																X		
Bone marrow aspirate/biopsy[h]	X							X						X		X	X		X	
Confirm eligibility	X	X																		
Laboratory Assessment																				
Hematology[i]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[j]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Coagulation (PT, INR, aPTT)	X																	X		
Hepatitis serologies[k]	X																			
Urinalysis[l]	X																	X		
Pregnancy test	X																			
Cerebrospinal fluid[m]																	X			
T/B/NK cell count[n]		X						X				X		X			X	X		
Biomarker - blood sample[o]		X		X		X		X				X		X		X	X	X	X	
Biomarker - bone marrow[p]	X							X						X [q]		X	X		X	
PK blood sampling[r]		X	X		X												(X)[s]			
Other																				
Survival status, incl. other malignancies																				X
Subsequent Anticancer Therapy																			X	X

Abbreviations: C=cycle; D or d=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-Treatment visit; LTFU=Long-Term Follow Up; PO=oral; RFU=Response Follow Up; TF=treatment failure; (X) = optional

Footnotes:

a. An EOT visit will occur 30 days (±7) from the last dose of study drug or prior to the start of a new anticancer treatment.
b. Subjects who discontinue for reasons other than TF will be followed every 3 months (±14 days) until TF or use of alternative anticancer treatment.
c. Concomitant medications are collected from within 14 days before first dose through the 30 days after the last dose of study drug.
d. See Section 11.4 for details regarding the reporting of AEs.
e. A complete physical examination will include, at a minimum, the general appearance of the subject, height (may use prior height measurement if available in source documents) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system.
f. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position for ≥3 minutes.
g. 12-lead ECG will be done in triplicate (≥1 minute apart). The calculated Fridericia's corrected QT interval (QTcF) average of the 3 ECGs must be <470 msec for eligibility. Subjects should be in a supine position and resting for at least 10 minutes before obtaining the ECGs. During the treatment period, ECG's may be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea. A single ECG tracing will be performed at EOT.
h. A unilateral bone marrow aspirate and biopsy will be done at Screening within 7 days before the first administration of study drug. Bone marrow aspirate/biopsy will be required Cycle 2 Day 1 (±3 days), Cycle 4 Day 1 (±3 days), then every 3 cycles (±5 days) (ie, Cycles 7, 10, and 13), and every 6 cycles (±5 days) thereafter until designation of treatment failure or withdrawal of consent. Subjects with prolonged pancytopenia and hypocellular bone marrow (ie, cellularity 5% or less without evidence of leukemia) at the Cycle 2 Day 1 assessment must undergo an additional bone marrow assessment on Day 42 (±3 days) after initiation of study treatment.
i. Hematology includes complete blood count with differential and platelet counts. Subjects with platelet counts ≤25,000/µL at baseline or during the first cycle will be required to have platelet assessment 3 times a week until the end of first treatment cycle. Thereafter, follow the Schedule of Assessment and hematological and dosing guidelines provided in Section 5.4.1.4).
j. Serum chemistry: Sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, uric acid, magnesium and bicarbonate.
k. Hepatitis C antibody, hepatitis B surface antigen and antibody and hepatitis B core antibody will be evaluated. If hepatitis B core antibody or hepatitis B surface antigen is positive, then hepatitis B PCR to quantitate hepatitis B DNA must be performed. DNA PCR needs to be confirmed negative (<29 U) prior to enrollment in subjects who are hepatitis B core antibody or hepatitis B surface antigen positive. For subjects who are hepatitis C antibody positive, hepatitis C PCR needs to be confirmed negative prior to enrollment.
l. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
m. In subjects who develop CNS progression, CSF will be obtained for PK, PD, and other disease related testing.
n. T/B/NK cell count samples are to be collected before dosing at the protocol specified timepoints.
o. Biomarker blood samples are to be collected before dosing at the protocol specified timepoints. On Day 1 of the ibrutinib run-in, blood sample will be collected at pre-dose and 4 hours (±30 min) after dosing with ibrutinib.
p. From the bone marrow biopsy, up to an additional 10 unstained slides and up to 20 mL aspirate samples will be collected for evaluation.
q. Bone marrow aspirate and biopsy including bone marrow smear slides (Cycles 7, 10, 13, then every 6 cycles thereafter)
r. Pharmacokinetic blood samples will be drawn according to the schedule Table 2. See Section 7.1.3.4 for more details regarding requested samples.
s. An additional PK blood sampling at TF visit would be required if CSF is drawn.

Appendix 2: Schedule of Assessments – Ibrutinib Monotherapy Cohort

Study Cycle		C1					C2				C3		C4		C5 & Beyond	TF	EOT[a]	RFU[b]	LTFU
Study Day		1	2	8	15	22	1	8	15	22	1	15	1	15	1				
							(±2 days)				(±2 days)		(±2 days)		(±2 days)	**Any time**	(±7d)	(±14 days)	
Study Drug Administration																			
Ibrutinib (continuous)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Procedure	**Screening** Day -28 to -1																		
Informed consent	X																		
Medical history & demographics	X	X																	
Review concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Review adverse events[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Complete physical exam & weight[e] *(height C1D1 only)*	X	X					X				X		X		X	X	X		
Symptom directed physical exam			X	X	X	X		X	X	X									
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X		
ECOG performance status	X	X			X		X		X	X	X		X		X	X	X	X	
Triplicate 12-Lead ECG[g]	X	If clinically indicated (eg, subjects with palpitations, lightheadedness)															X		
Bone marrow aspirate/biopsy[h]	X						X						X		X	X		X	
Confirm eligibility	X	X																	
Laboratory Assessment																			
Hematology[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Coagulation (PT, INR, aPTT)	X																X		
Hepatitis serologies[k]	X																		
Urinalysis[l]	X																X		
Pregnancy test	X																		
Cerebrospinal fluid[m]																X			
T/B/NK cell count[n]		X					X				X		X			X	X		
Biomarker - blood sample[o]		X			X		X				X		X		X	X	X	X	
Biomarker - bone marrow[p]	X						X						X		X[q]	X		X	
PK blood sampling[r]		X	X	X												(X[s])			
Other																			
Survival status, incl. other malignancies																			X
Subsequent anticancer therapy																		X	X

Abbreviations: C=cycle; D or d =day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-Treatment visit; LTFU=Long-Term Follow Up; PO=oral; RFU=Response Follow Up; TF=treatment failure; (X) = optional

Footnotes:

a. An EOT visit will occur 30 days. (±7) from the last dose of study drug or prior to the start of a new anticancer treatment.
b. Subjects who discontinue for reasons other than TF will be followed every 3 months (±14 days) until TF or use of alternative anticancer treatment.
c. Concomitant medications are collected from within 14 days before first dose through the 30 days after the last dose of study drug.
d. See Section 11.4 for details regarding the reporting of AEs.
e. A complete physical examination will include, at a minimum, the general appearance of the subject, height (C1D1 Visit only [may use prior height measurement if available in source documents]) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system.
f. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position for ≥3 minutes.
g. 12-lead ECG will be done in triplicate (≥1 minute apart). The calculated Fridericia's corrected QT interval (QTcF) average of the 3 ECGs must be <470 msec for eligibility. Subjects should be in a supine position and resting for at least 10 minutes before obtaining the ECGs. During the treatment period, ECG's may be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea. A single ECG tracing will be performed at EOT.
h. A unilateral bone marrow aspirate and biopsy will be done at Screening or within 7 days before the first administration of study drug. Bone marrow aspirate/ biopsy will be required Cycle 2 Day 1 (±3 days), Cycle 4 Day 1 (±3 days), then every 3 cycles (±5 days) (ie, Cycles 7, 10, and 13), and every 6 cycles (±5 days) thereafter until designation of TF or withdrawal of consent. Subjects with prolonged pancytopenia and hypocellular bone marrow (ie, cellularity 5% or less without evidence of leukemia) at the C2D1 assessments must undergo an additional bone marrow assessment on Day 42 (±3 days) after initiation of study treatment.
i. Hematology includes complete blood count with differential and platelet counts. Subjects with platelet counts ≤25,000/µL at baseline or during the first cycle will be required to have platelet assessment 3 times a week until the end of first treatment cycle. Thereafter, follow the Schedule of Assessment and hematological and dosing guidelines provided in Section 5.4.1.4).
j. Serum chemistry: sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, uric acid, magnesium and bicarbonate.
k. Hepatitis C antibody, hepatitis B surface antigen and antibody and hepatitis B core antibody will be evaluated. If hepatitis B core antibody or hepatitis B surface antigen is positive, then hepatitis B PCR to quantitate hepatitis B DNA must be performed. DNA PCR needs to be confirmed negative (<29 U) prior to enrollment in subjects who are hepatitis B core antibody or hepatitis B surface antigen positive. For subjects who are hepatitis C antibody positive, hepatitis C PCR needs to be confirmed negative prior to enrollment.
l. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
m. In subjects who develop CNS progression, CSF will be obtained for PK, PD, and other disease related testing.
n. T/B/NK cell count samples are collected before dosing at the protocol specified timepoints.
o. Biomarker blood samples are collected before dosing at the protocol specified timepoints.
p. From the bone marrow biopsy, up to an additional 10 unstained slides and up to 20 mL aspirate samples will be collected for evaluation.
q. Bone marrow aspirate and biopsy including bone marrow smear slides (Cycles 7, 10, 13, then every 6 cycles thereafter)
r. Pharmacokinetic blood samples will be drawn according to the schedule Table 3. See Section 7.1.3.4 for more details regarding requested samples.
s. An additional PK blood sampling at TF visit would be required if CSF is drawn.

Appendix 3: Schedule of Assessments – Ibrutinib + Azacitidine Combination Cohort (Cohort 3)

Study Cycle		Ibrutinib Run-in	C1				C2				C3		C4		C5 & Beyond	TF	EOT[a]	RFU[b]	LTFU
Study Day		1	1	7	15	22	1	7	15	22	1	15	1	15	1				
							(±2 days)				(±2 days)		(±2 days)		(±2 days)	**Any time**	(±7d)	(±14 days)	
Study Drug Administration																			
Ibrutinib (continuous)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Azacitidine (for 7 days every 4 wks)			Days 1-7				Days 1-7				Days 1-7		Days 1-7		Days 1-7				
Procedure	**Screening** Day -28 to -1																		
Informed consent	X																		
Medical history & demographics	X	X																	
Review Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Review adverse events[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Complete Physical Exam & Weight[e]	X	X					X				X		X		X	X	X		
Symptom directed physical exam				X	X	X		X	X	X									
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X		
ECOG performance status	X	X			X		X		X		X		X		X	X	X	X	
Triplicate 12-Lead ECG[g]	X	If clinically indicated (eg, subjects with palpitations, lightheadedness)															X		
Bone marrow aspirate/biopsy[h]	X						X						X		X	X		X	
Confirm eligibility	X	X																	
Laboratory Assessment																			
Hematology[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Coagulation (PT, INR, aPTT)	X																X		
Hepatitis serologies[k]	X																		
Urinalysis[l]	X																X		
Pregnancy test	X																		
Cerebrospinal fluid[m]																X			
T/B/NK cell count[n]		X					X				X		X			X	X		
Biomarker - blood sample[o]		X	X		X		X				X		X		X	X	X	X	
Biomarker - bone marrow[p]	X						X						X		X [q]	X		X	
PK blood sampling[r]		X	X	X												(X)[s]			
Other																			
Survival status, incl. other malignancies																			X
Subsequent Anticancer Therapy																		X	X

Abbreviations: C=cycle; D or d=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-Treatment visit; LTFU=Long-Term Follow Up; PO=oral; RFU=Response Follow Up; TF=treatment failure; (X) = optional

Footnotes:

a. An EOT visit will occur 30 days (±7) from the last dose of study drug or prior to the start of a new anticancer treatment.
b. Subjects who discontinue for reasons other than TF will be followed every 3 months (±14 days) until TF or use of alternative anticancer treatment.
c. Concomitant medications are collected from within 14 days before first dose through the 30 days after the last dose of study drug.
d. See Section 11.4 for details regarding the reporting of AEs.
e. A complete physical examination will include, at a minimum, the general appearance of the subject, height (may use prior height measurement if available in source documents) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system.
f. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position for ≥3 minutes.
g. 12-lead ECG will be done in triplicate (≥1 minute apart). The calculated Fridericia's corrected QT interval (QTcF) average of the 3 ECGs must be <470 msec for eligibility. Subjects should be in a supine position and resting for at least 10 minutes before obtaining the ECGs. During the treatment period, ECG's may be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea. A single ECG tracing will be performed at EOT.
h. A unilateral bone marrow aspirate and biopsy will be done at Screening within 7 days before the first administration of study drug. Bone marrow aspirate/biopsy will be required Cycle 2 Day 1 (±3 days), Cycle 4 Day 1 (±3 days), then every 3 cycles (±5 days) (ie, Cycles 7, 10, and 13), and every 6 cycles (±5 days) thereafter until designation of treatment failure or withdrawal of consent. Subjects with prolonged pancytopenia and hypocellular bone marrow (ie, cellularity 5% or less without evidence of leukemia) at the Cycle 2 Day 1 assessment must undergo an additional bone marrow assessment on Day 42 (±3 days) after initiation of study treatment.
i. Hematology includes complete blood count with differential and platelet counts. Subjects with platelet counts ≤25,000/µL at baseline or during the first cycle will be required to have platelet assessment 3 times a week until the end of first treatment cycle. Thereafter, follow the Schedule of Assessment and hematological and dosing guidelines provided in Section 5.4.1.4).
j. Serum chemistry: Sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, uric acid, magnesium and bicarbonate.
k. Hepatitis C antibody, hepatitis B surface antigen and antibody and hepatitis B core antibody will be evaluated. If hepatitis B core antibody or hepatitis B surface antigen is positive, then hepatitis B PCR to quantitate hepatitis B DNA must be performed. DNA PCR needs to be confirmed negative (<29 U) prior to enrollment in subjects who are hepatitis B core antibody or hepatitis B surface antigen positive. For subjects who are hepatitis C antibody positive, hepatitis C PCR needs to be confirmed negative prior to enrollment.
l. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
m. In subjects who develop CNS progression, CSF will be obtained for PK, PD, and other disease related testing.
n. T/B/NK cell count samples are to be collected before dosing at the protocol specified timepoints.
o. Biomarker blood samples are to be collected before dosing at the protocol specified timepoints. On Day 1 of the ibrutinib run-in, blood sample will be collected at pre-dose and 4 hours (±30 min) after dosing with ibrutinib.
p. From the bone marrow biopsy, up to an additional 10 unstained slides and up to 20 mL aspirate samples will be collected for evaluation.
q. Bone marrow aspirate and biopsy including bone marrow smear slides (Cycles 7, 10, 13, then every 6 cycles thereafter)
r. Pharmacokinetic blood samples will be drawn according to the schedule Table 4. See Section 7.1.3.4 for more details regarding requested samples.
s. An additional PK blood sampling at TF visit would be required if CSF is drawn.

Appendix 4: ECOG Status Scores

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

**Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Available at: http://www.ecog.org/general/perf_stat.html. Accessed January 04, 2008.

Appendix 5: Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A are defined as follows. Refer to Section 6.2.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib. Further information can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	carbamazepine
indinavir	efavirenz
nelfinavir	nevirapine
ritonavir	barbiturates
clarithromycin	glucocorticoids
itraconazole	modafinil
ketoconazole	oxcarbarzepine
nefazodone	phenobarbital
saquinavir	phenytoin
suboxone	pioglitazone
telithromycin	rifabutin
cobicistat	rifampin
boceprevir	St. John's Wort
mibefradil	troglitazone
telaprevir	
troleandomycin	
posaconazole	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir/ritonavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
gestodene	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

Appendix 6: Response Criteria

Category	Definition
Complete Remission (CR)*	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0 x 10^9/L (1000/µL); platelet count >100 x 10^9/L (100 000/µL); independence of red cell transfusions
CR with Incomplete Recovery (CRi)	All CR criteria except for residual neutropenia (< 1.0 x 10^9/L [1000/µL]) or thrombocytopenia (<100 x 10^9/L [100 000/µL])
Morphologic leukemia-free state	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial Remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Relapse	Bone marrow blasts > 5%; or reappearance of blasts in the blood; or development of extramedullary disease

Reference: Döhner 2010

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

Appendix 7: Child-Pugh Score for Subjects with Liver Impairment

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Source:

1. Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, et al . “Transection of the oesophagus for bleeding oesophageal varices”. The British journal of surgery, 1973;60: 646-9.