IST PROTOCOL	
Title:	**A Phase 2 Study of Ibrutinib and Blinatumomab in Relapsed and Refractory B-Cell Acute Lymphoblastic Leukemia**
Protocol Number:	UCDCC#266 (PCYC: #20265)
Study Drugs:	Ibrutinib (PCI-32765) and Blinatumomab
Coordinating Center:	University of California, Davis Comprehensive Cancer Center Office of Clinical Research 4501 X Street, Sacramento, CA 95817 [redacted]
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IND #/ IND Sponsor:	133510/ University of California Davis Comprehensive Cancer Center
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Participating Centers:	Site PI: George Yaghmour, MD USC/Norris Comprehensive Cancer Center University of Southern California [redacted]

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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Signature of Principal Investigator

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Date

_____
Printed Name of Principal Investigator

Institution Name: _____

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, instructions from Pharmacyclics representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

LIST OF IN-TEXT TABLES AND FIGURES

SYNOPSIS

Study Title:	**A Phase 2 Study of Ibrutinib and Blinatumomab in Relapsed and Refractory B-Cell Acute Lymphoblastic Leukemia**
Protocol Number:	UCDCC#266
Study Phase:	2
Study Duration:	3 years
Investigational Product and Reference Therapy:	Ibrutinib will be supplied as 70 mg or 140 mg hard gelatin capsules for oral (PO) administration. Blinatumomab will be given as standard of care and is commercially available.
Objectives:	**Primary Objective:** The primary objective is to evaluate the efficacy of ibrutinib and blinatumomab in patients with relapsed or refractory B-ALL as measured by complete response (CR) rate. **Secondary Objectives**: The secondary objective is to further examine the efficacy and safety of ibrutinib and blinatumomab in patients with relapsed or refractory B-ALL as measured by overall response rate (ORR, defined as CR plus CR with incomplete count recovery [CRi], or CR plus CR with partial hematologic recovery [CRh]), relapse free survival (RFS), overall survival (OS), minimal residual disease (MRD) response, proportion of patients bridged to allogeneic hematopoietic cell transplant (allo-HCT), and toxicity. **Exploratory Objectives:** The exploratory objectives are to examine the pharmacodynamic effects of ibrutinib and blinatumomab in patients with relapsed or refractory B-ALL as measured by BTK and ITK expression and occupancy analysis and immune correlative analysis (including plasma cytokines, flow cytometric analysis of T cell subsets and NK cells, and T cell functional assays).
Study Design:	This is a non-randomized open-label prospective phase 2 study of the combination of ibrutinib with blinatumomab in subjects with relapsed or refractory B-ALL. The study will consist of two parts. In the first part, a safety lead-in cohort will test ibrutinib 560mg in combination with blinatumomab in the first 6-9 patients. In the second part, up to 18 subjects (including subjects in safety lead-in cohort) will be treated.
Population:	This study will enroll adult subjects with a confirmed diagnosis of relapsed or refractory B-ALL with measurable bone marrow lymphoblasts or biopsy-proven extramedullary site measurable by CT or PET/CT imaging. Ph+ B-ALL patients must have failed treatment with at least one second generation tyrosine kinase inhibitor. Subjects with B-ALL in remission with less than 5% blasts with minimal residual disease greater than or equal to 0.1% will also be enrolled.

Inclusion Criteria: *Refer to Section 4 for the complete and detailed list of inclusion/exclusion criteria.*	*Disease Related* 1. Pathologically confirmed diagnosis of relapsed or refractory B-cell acute lymphoblastic leukemia/lymphoma with measurable bone marrow lymphoblasts or biopsy-proven extramedullary site measurable by CT or PET/CT imaging. Philadelphia chromosome-positive (Ph+) B-ALL patients must have failed treatment with at least one second generation tyrosine kinase inhibitor. Subjects with B-ALL in remission with less than 5% blasts, with or without count recovery, but with minimal residual disease (MRD) greater than or equal to 0.1% are eligible. Prior allo-HCT is allowed. *Laboratory* 2. No Hematologic parameters for inclusion. Transfusion-dependent patients are eligible and platelet counts should be maintained greater than 10,000/mm3 throughout cycles 1 and 2. 3. Adequate hepatic and renal function defined as: a. Bilirubin less than or equal to 1.5 x upper limit of normal (ULN) (unless bilirubin rise is due to Gilbert's syndrome or B-ALL or non-hepatic origin). b. Serum aspartate transaminase (AST) or alanine transaminase (ALT) less than or equal to 3 x ULN (unless due to B-ALL) c. Estimated Creatinine Clearance greater than or equal to 30 ml/min (Cockcroft-Gault) or serum creatinine less than or equal to 2 x ULN. 4. PT/INR ≤1.5 x ULN and PTT (aPTT) ≤1.5 x ULN (unless B-ALL related). *Demographic* 5. Men and women ≥ 18 years of age. 6. Karnofsky Performance Status (KPS) performance status of 60% or greater. *Ethical/Other* 7. Ability to understand and willingness to sign an informed consent form. 8. Ability to adhere to the study visit schedule and other protocol requirements. 9. Female subjects who are of non-reproductive potential (i.e., 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 childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to the first study drug administration. 10. Male and female subjects who agree to use both a highly effective method of birth control (e.g., implants, injectables, combined

	oral contraceptives, some intrauterine devices [IUDs], complete abstinence[1], or sterilized partner) and a barrier method (e.g., condoms, vaginal ring, sponge, etc.) during the period of therapy and for 90 days after the last dose of study drug. 11. Eligibility of patients receiving any medications or substances known to affect or with the potential to affect the activity or pharmacokinetics of ibrutinib or blinatumomab will be determined following review of their case by the Investigator.
Exclusion Criteria:	<u>Disease-Related</u> 1. Diagnosis of T-ALL or Burkitt's Leukemia/Lymphoma. 2. Patients with current evidence of active CNS leukemia. <u>Concurrent Conditions</u> 3. History of treatment with ibrutinib or blinatumomab. 4. Investigational therapy, chemotherapy, immunotherapy, radiotherapy, or systemic GVHD therapy within two weeks or five half-lives (whichever is shorter). Steroids, hydroxyurea and/or leukapheresis are allowed to control blast count prior to the first dose of study drug. 5. Prior allo-HCT less than three months from the time of enrollment. 6. Any active acute GVHD or chronic GVHD greater than Grade 1. 7. History of allergic reactions attributed to compounds of similar chemical or biologic composition to ibrutinib and blinatumomab or other agents used in this study. 8. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug. 9. Recent culture-documented infection requiring intravenous antimicrobials that was completed ≤7 days before the first dose of study drug or any uncontrolled active systemic infection. Fever of unknown origin is not an exclusion criterion, as this may be disease-related. 10. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE v4.03), Grade ≤2, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.

[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

	11. Known bleeding disorders (e.g., von Willebrand's disease) or hemophilia. 12. History of stroke or intracranial hemorrhage within 6 months prior to enrollment. 13. Active infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. Subjects with HIV must have a CD4 count at or above the institutional lower limit of normal and not taking prohibited CYP3A strong inhibitors. 14. Major surgery within 4 weeks of first dose of study drug. 15. Any life-threatening illness, medical condition, or organ system dysfunction, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, active autoimmune disorder, or psychiatric illness/social situations that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk. 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 enrollment. 16. History of other malignancies, except for malignancy surgically resected (or treated with other modalities) with curative intent, adequately treated in situ carcinoma of the breast or cervix uteri, basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin. Malignancy treated with curative intent with no known active disease present for > 3 years. 17. Concomitant use of warfarin or other Vitamin K antagonists. 18. Subjects who received a strong cytochrome P 450 (CYP) 3A inhibitor within 7 days prior to the first dose of ibrutinib or subjects who require continuous treatment with a strong CYP3A inhibitor (see Appendix 3). 19. Subjects with chronic liver disease with hepatic impairment Child-Pugh class B or C (see Appendix 4). 20. Breastfeeding or pregnant. 21. Participation in clinical trials with other investigational agents not included in this trial throughout the duration of this trial. 22. Unwilling or unable to participate in all required study evaluations and procedures or 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:	The first two cycles will be considered induction therapy. Subjects achieving a CR/CRi during induction will be able to receive up to three additional cycles of consolidation, for a total of five cycles. Treatment with ibrutinib will continue until either disease progression OR withdrawal of informed consent OR unacceptable or intolerable toxicities. Blinatumomab dosing is per standard of care. Cycle 1 (49 days): Ibrutinib 560mg PO daily days 1-49 Blinatumomab 9mcg/day CIV days 8-14 Blinatumomab 28mcg/day CIV days 15-35 Cycles 2-5 (42 days/cycle): Ibrutinib 560mg PO daily days 1-42 Blinatumomab 28mcg/day CIV days 1-28 Maintenance Ibrutinib (28 days/cycle): Ibrutinib 560mg PO daily days 1-28
Concomitant Therapy:	Refer to Section 6 for information on concomitant therapy.
Safety Plan:	Analysis of safety data will be conducted on the all treated population, which includes enrolled subjects who receive at least 1 dose of ibrutinib. Safety will be reviewed continuously. Adverse events and serious adverse events (SAEs) will be reviewed by the Data and Safety Monitoring Committee on an ongoing basis to identify safety concerns.
Statistical Methods and Data Analysis:	**Primary Efficacy Analysis:** The primary objective is to evaluate the efficacy of ibrutinib and blinatumomab in patients with relapsed or refractory B-ALL. The primary endpoint is the rate of complete response (CR) within the first two cycles. Subjects who discontinue study therapy before the end of two cycles because of disease progression, death or adverse events related to treatment will be considered in the primary endpoint analysis. Determination of response will be made by the Investigator according to the NCCN Guidelines for Acute Lymphoblastic Leukemia, Version 2.2015. Response criteria for lymph node and other extramedullary disease are derived from the International Working Group revised response criteria for malignant lymphoma (38). **Secondary Efficacy Analysis:** The secondary objective is to further examine the efficacy and safety of ibrutinib and blinatumomab in patients with relapsed or refractory B-ALL. Secondary endpoints include toxicity (graded according to the NCI CTCAE version 4.03 with DLTs defined as per Section 5.2.3), overall response rate (ORR, defined as CR plus CR with incomplete count recovery [CRi], or CR plus CR with partial hematologic recovery [CRh], as defined by disease-specific response criteria), relapse free survival

	(RFS, as measured by the time of CR/CRi until the date of progression or death from any cause), overall survival (OS, as measured from the time of first study drug administration until the date of progression or death from any cause), minimal residual disease (MRD) response (defined as B-ALL cells comprising greater than 0.01% of bone marrow mononuclear cells [BMMC] as measured by flow cytometry or molecular studies), and proportion of patients bridged to allo-HCT). Data for subjects who have not died will be censored at the date of last known contact for calculation of OS and RFS. **Exploratory Efficacy Analysis:** The exploratory objectives are to examine the pharmacodynamic effects of ibrutinib and blinatumomab in patients with relapsed or refractory B-ALL. Exploratory endpoints are BTK and ITK expression and occupancy analysis and immune correlative analyses (plasma cytokines, flow cytometric analysis of T cell subsets and NK cells, and T cell functional assays). **Safety Analysis:** Analysis of safety data will be conducted on the 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. The safety analyses will be based on the monitoring of adverse events, survival status, 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, vital signs measurements, and reason for discontinuation of study drug (if applicable). Tables will be created to summarize the toxicities and adverse effects by dose, course, organ and severity. Descriptive statistics will be used, including mean, standard deviation, median, and minimum and maximum values for continuous variables and frequencies and percentages for categorical variables. No formal statistical testing is planned. The first part of the study will be a safety-lead in cohort comprising the first 6-9 patients enrolled and treated. The rules of this cohort are described in Section 5.2.2 and 5.2.3. The intended study dose of ibrutinib 560mg in combination with blinatumomab will be tested in the first 6 patients. If 0-1 dose limiting toxicities (DLTs) are observed then the study will continue to accrue as per the Simon's two-stage design (Section 10.3). If 2 DLTs are observed in the first 6 patients, then 3 additional subjects will be assessed for DLTs. If 3 or more of the 9 subjects experience DLTs, enrollment will be halted at the 560mg dose level and an ibrutinib dose of 420mg will be considered. For the safety lead-in, if patients do not experience a DLT during cycle 1 but miss more than 25% of the total planned treatment doses for the cycle, they will be replaced.

Interim Analysis	• After the first 6-9 subjects are evaluable for safety, the first interim analysis will evaluate whether DLTs have occurred and whether the study can be continued. • After the first 11 subjects are evaluable for response (including the 6-9 patients in the safety lead-in phase), an interim analysis of the primary endpoint of CR rate will be performed. The study will continue if there are more than four responses as per the Simon's two-stage design of the study.
Sample Size Determination	The primary endpoint for this study is CR rate. A 30% increase in CR rate compared to historical control with addition of ibrutinib would be clinically significant. A Simon's minimax two-stage design will be used. The null hypothesis that the true CR rate is 33% (historical control from Topp et al. Lancet Oncology 2015) will be tested against a one-sided alternative. In the first stage, 11 patients will be accrued (including the 6-9 patients from the safety lead-in). If there are 4 or fewer responses in these 11 patients, the study will be stopped. Otherwise, 7 additional patients will be accrued for a total of 18. The null hypothesis will be rejected if 10 or more responses are observed in 18 patients. This design yields a type I error rate of 0.05 and power of 0.8 when the true complete response rate is 63%. Thus, the study will have a minimum sample size of 9 subjects and a maximum of 18 subjects. There will be 6-9 subjects in the safety lead-in cohort, and pending the interim analysis of response as per the Simon's two-stage design there will be a maximum of 18 subjects. The total sample size is 20, accounting for the possibility of subject drop out.

ABBREVIATIONS

AE	adverse event
AESI	Adverse Events of Special Interest (AESI)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCR	B-cell receptor
BTK	Bruton's tyrosine kinase
CLL	chronic lymphocytic leukemia
Cmax	maximum observed plasma concentration
CR	complete response
CrCl	creatinine clearance
CRF	case report form (paper or electronic as appropriate for this study)
CTCAE	NCI Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
IAC	Interim Analysis Committee
IB	Investigator's Brochure
IC50	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
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRU	medical resource utilization
MTD	maximum tolerated dose
PCR	polymerase chain reaction
PD	progressive disease
P-gp	P-glycoprotein
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
aPTT	activated partial thromboplastin time
PT	prothrombin time
QTc	QT interval corrected for heart rate
SAE	serious adverse event
SLL	small lymphocytic lymphoma
t1/2	half-life
Tmax	time to maximum plasma concentration
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
ULN	upper limit of normal

1. BACKGROUND

1.1. Disease/Histology

B-cell acute lymphoblastic leukemia/lymphoma (B-ALL) is a heterogeneous group of aggressive lymphoid malignancies. Although often thought of as a pediatric disease, B-ALL is the most common subtype of ALL in patients older than 60, accounting for 75-89% of cases (1). The Philadelphia chromosome [t(9;22)(q34;q11)] is the most frequent cytogenetic aberration in adults with B-ALL, occurs in 20-30% of adult patients and is associated with inferior outcomes (2). B-ALL is often subdivided into Philadelphia chromosome positive (Ph+) and negative (Ph-) B-ALL. Overall, B-ALL prognosis is determined by age, cytogenetics and molecular mutations, immunophenotype and level of minimal residual disease after treatment. Initial treatment is often effective, even in patients with Ph+ B-ALL and older patients. For example, the hyper-CVAD regimen produces complete remission (CR) rates around 90% and cures about 40-50% of patients (3). However, long-term survival in adults is only 35-45%, and the predominant reason for failure is disease recurrence (4). Outcomes for salvage chemotherapy for relapsed or refractory B-ALL, including Ph+ B-ALL after failure of prior second generation tyrosine kinase inhibitors (TKI), are poor, with CR rates of 20-30% and median overall survival (OS) of 3-6 months (5). Allogeneic hematopoietic cell transplant (allo-HCT) is the only curative option for these patients, and achievement of CR is required before allo-HCT (5, 6). New therapeutic approaches to improve rates of CR and minimal residual disease (MRD) negative CR are required to improve the chances of eligibility for allo-HCT and potential for cure for patients with relapsed and refractory B-ALL.

1.1.1. Treatment Options

The B-lineage surface antigen CD19 is expressed in more than 95% of B-ALL blasts, making it a promising target for immunotherapy (7). Blinatumomab (BLINCYTO®, Amgen) is a bispecific T-cell engager (BiTE) antibody construct that has dual specificity for CD19 and CD3 and is FDA approved for the treatment of Ph- relapsed or refractory B-ALL (8). Simultaneous binding to CD19-positive cells and CD3-positive cytotoxic T cells leads to redirected T-cell-mediated lysis of CD19-positive cells through formation of a cytolytic synapse (9). Preliminary activity for blinatumomab in relapsed and refractory B-ALL was seen in initial studies (10, 11). In a larger, multicenter phase 2 study with 189 relapsed or refractory B-ALL patients, the rate of CR within the first 2 cycles was 33% (12). Most responses were seen in cycle 1. Treatment was well tolerated with the most frequent grade 3 or worse adverse events (AEs) being febrile neutropenia (25%), neutropenia (16%), and anemia (14%). Cytokine release syndrome was seen in 2% of subjects. Eighty-two percent of patients had an MRD response in cycles 1-2, and 40% were able to proceed to potentially curative allo-HCT. A dexamethasone prephase treatment was allowed, but it had no effect on outcomes. Median relapse-free survival was 6.9 months for patients in CR, and median OS was 6.1 months. Blinatumomab was also shown to have similar activity in Ph+ B-ALL, as compared to Ph- B-ALL, after failure of second-generation TKI with 31% of subjects achieving CR within the first two cycles (13). Subsequent analyses from the Topp et al.

study showed that patients with less than 50% bone marrow blasts and patients with higher CD3-positive cells at the time of initiation of blinatumomab therapy were more likely to respond (14, 15). For example, the response rate was 73% versus 29% in subjects with pretreatment bone marrow lymphoblasts of less than 50% or 50% or more, respectively, in the Topp et al. study (12). This suggests that the combination of blinatumomab with an agent or agents that will potentially decrease tumor burden and activate T-cell responses could have synergistic activity with blinatumomab and improve salvage outcomes.

1.1.2. Role of BTK in Disease/Histology

Bruton's Tyrosine Kinase (BTK) is a tyrosine kinase that is predominantly expressed in hematopoietic cells, except T-cells and plasma cells, and is a central player in the B-cell antigen receptor (BCR) signaling pathway (16). It is expressed throughout B-cell differentiation, including early precursor B-cell stages (17). BTK plays a key role in proliferation, survival, and differentiation signaling cascades from multiple cell surface receptors, including G-protein coupled receptors, toll-like receptors, and B-cell receptors (16). BTK inhibition with the irreversible inhibitor ibrutinib (IC50 0.5nM) has demonstrated exceptional activity in B-cell malignancies through inhibition of the B-cell receptor pathway (18, 19). Early-phase trials with ibrutinib in relapsed/refractory B-cell malignancies have shown remarkable safety and efficacy as a single agent or in combination with R-CHOP chemoimmunotherapy (18, 20, 21). Dose-limiting events were not seen up to doses as high as 840mg daily, and full occupancy of BTK was demonstrated at doses as low as 2.5mg/kg/day. These studies demonstrated a favorable toxicity profile as well with cytopenias, febrile neutropenia, and infections being more common adverse effects.

BTK is required for pre-BCR-dependent survival and anti-apoptosis signaling in B-cell precursors (22, 23). Furthermore, BTK couples B-cell activating factor receptor (BAFF-R), which is expressed in B-ALL cells but not normal pre-B cells, to NF-kB downstream signaling and inhibition of BAFF-R reduces cell viability and proliferation of B-ALL cells (24, 25). Inhibition of Spleen Tyrosine Kinase (Syk), upstream of BTK in the same BCR signaling pathway, by potent Syk inhibitors such as fostamatinib and BAY61-3606 has also shown significant preclinical activity in B-ALL (26).

1.2. Investigational Product Name and Description

Ibrutinib will be supplied by Pharmacyclics.

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK) co-developed by Pharmacyclics LLC and Janssen Research & Development 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 have 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, first-line treatment of patients with CLL 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 (27).

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.

1.3. Summary of Nonclinical Data

For the most comprehensive nonclinical information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

1.3.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the BTK (28). 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 B-cell receptor and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (29).

Preclinical data suggests ibrutinib has activity in B-ALL. BTK was expressed in 12 of 14 B-cell ALL (B-ALL) cell lines and 5 of 5 adult B-ALL patient samples (30). Cultured cell viability and proliferation was decreased by ibrutinib in all BTK-expressing cell lines with an IC50 of at least <3.5uM. In addition, cultured patient samples showed ibrutinib-induced apoptosis at levels consistent with CLL samples. Ibrutinib 560mg was tested clinically in a Phase 2 study in relapsed or refractory B-ALL (NCT02129062). The study was terminated early due to poor accrual with no reported safety concerns to date. The 560mg dose level is also being explored in other aggressive diseases, such as AML (NCT02351037) and full BTK occupancy has been shown in various diseases at that dose level. Furthermore, an earlier Phase 1 study showed that ibrutinib up to 840mg daily was tolerated without dose-limiting toxicity.

Importantly, ibrutinib also inhibits several other kinases with an IC50 in the nanomolar range, including Interleukin-2-inducible T-cell kinase (ITK). ITK is another member of the Btk family of tyrosine kinases that plays an important role in T-cell receptor signaling and promotes Th2 immunity (31, 32). Ibrutinib binds irreversibly to ITK and inhibits signaling through ITK at concentrations achieved with dosing in B-cell clinical trials. Furthermore, the IC50 for ibrutinib

and ITK is higher than BTK suggesting higher doses of ibrutinib, such as 560mg, are more likely to inhibit ITK. ITK inhibition leads to a subversion of Th2 immunity, and promotes Th1-based (CD3+CD8+ cytotoxic T-cell) immune responses. Dubovsky et al. used a mouse chronic lymphocytic leukemia model inoculated with Listeria, which stimulates a Th1-based immune response (31). Presence of CLL rendered the mouse less responsive to the Listeria inoculation, as measured by Listeria-specific CD8-positive cytotoxic T-cells. Pre-treatment of the CLL mouse model with ibrutinib for one week prior to inoculation led to an approximately 2.5-fold increase in Listeria-specific CD8-positive cytotoxic T-cells when measured 8 days after inoculation. Importantly, higher levels of CD3+CD8+ T cells predict a higher response to blinatumomab in B-ALL suggesting a lead-in period with ibrutinib may enhance the activity of blinatumomab via this immunomodulatory effect. Further evidence for the role of ibrutinib as an immunomodulatory molecule has recently been published. In one study, ibrutinib increased the effectiveness of PD-1/PD-L1 blockade, and in a second study, ibrutinib enhanced the engraftment and activity of CD19 CAR-T cells (32, 33). Overall, there is mounting evidence for the off-target immunomodulatory effects of ibrutinib, likely mediated through ITK, which could improve its effectiveness in diseases amenable to immune-based treatment approaches, such as B-ALL.

For more detailed and comprehensive information regarding nonclinical pharmacology, refer to the current Investigator's Brochure.

1.3.2. Toxicology

In safety pharmacology assessments, 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 20 times the exposure (area under the concentration-time curve [AUC]) in patients administered the dose of 560 mg daily and 420 mg, respectively. Fetal loss and reduced fetal body weights were also seen in treated pregnant animals.

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

1.3.2.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

1.4. Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

1.4.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half-life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 13 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Despite the doubling in mean systemic exposure when dosed with food, the favorable safety profile of ibrutinib allows dosing 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.

1.4.1.1. Summary of Clinical Safety

A brief summary of safety data from monotherapy and combination therapy studies is provided in 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 (e.g., USPI, SmPC).

Pooled safety data for a total of 1318 subjects treated with ibrutinib monotherapy from 13 studies that have completed primary analysis or final analysis as of the 31 May 2016 cutoff date for the current IB update in B-cell malignancies are summarized below.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1318):

Most frequently reported TEAEs ≥ 15% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥ 3%	Most frequently reported Serious TEAEs ≥ 2%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Pyrexia	Hypertension	
Anemia	Diarrhea	
Neutropenia	Atrial fibrillation	
Upper respiratory tract infection		
Thrombocytopenia		
Oedema peripheral		

[a] Source is Table 6 of IB (v10), [b] Source is Table 8 of IB (v10), [c] Source is Table 9 of IB (v10).

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 ≥ 20% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥ 3% [b]	Most frequently reported Serious TEAEs ≥ 2% [c]
Neutropenia	Neutropenia	Pneumonia
Diarrhea	Thrombocytopenia	Febrile neutropenia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Neutrophil count decreased	Cellulitis
Anemia	Anemia	
Pyrexia	Fatigue	
	Hypertension	
	Diarrhea	

[a] Source is Table 10 of IB (v10), [b] Source is Table 12 of IB (v10), [c] Source is Table 13 of IB (v10).

For more detailed information refer to the current version of the IB.

1.4.2. Risks

1.4.2.1. Bleeding-Related Events

There have been reports of bleeding events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor bleeding events such as contusion, epistaxis, and petechiae; and major bleeding events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria.

In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed, refer to Section 6.2.4. Use of either anticoagulants or antiplatelet agents concomitantly with ibrutinib increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Monitor for signs or symptoms of bleeding. See Section 6.2.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. Supplements such as fish oil and vitamin E preparations should be avoided.

Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding. See Section 6.4 for guidance on ibrutinib management with surgeries or procedures. Subjects with congenital bleeding diathesis have not been studied.

1.4.2.2. Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/mcL) may confer increased risk. Consider temporarily withholding ibrutinib. Subjects should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

1.4.2.3. Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these reported infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

1.4.2.4. Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Subjects should be monitored for fever, weakness, or easy bruising and/or bleeding.

1.4.2.5. Cardiac Arrhythmias

Fatal and serious cardiac arrhythmias or cardiac failure have occurred in patients treated with ibrutinib. Patients with significant cardiac comorbidities may be at greater risk of events, including sudden fatal cardiac events. Atrial fibrillation, atrial flutter, ventricular tachyarrhythmia, and cardiac failure, have been reported, particularly in patients with acute infections, or cardiac risk factors including hypertension, diabetes mellitus, and a previous history of cardiac arrhythmia.

Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating ibrutinib. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Consider further evaluation (e.g., ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns. For signs and symptoms that persist, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines (see Section 5.3.1.4).

1.4.2.6. Non-Melanoma Skin Cancer

Non-melanoma skin cancers have occurred in patients treated with ibrutinib. Monitor patients for the appearance of non-melanoma skin cancer.

1.4.2.7. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been reported with ibrutinib therapy. Subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor subjects closely and take appropriate precautions.

1.4.2.8. 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 and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.3.1.4).

1.4.2.9. Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Rash occurred at a higher rate in the ibrutinib arm than in the ofatumumab arm in Study 1112. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs

and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

1.4.2.10. Lymphocytosis

Upon initiation of single agent treatment with ibrutinib, a reversible increase in lymphocyte counts (i.e., ≥50% increase from baseline and an absolute count >5,000/mcL), often associated with reduction of lymphadenopathy, has been observed in most subjects (66%) with CLL/SLL. This effect has also been observed in some subjects (35%) 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 month of ibrutinib therapy and typically resolves within a median of 8 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL (range, 0.1 to 104 weeks).

When ibrutinib was administered in combination with BR or with obinutuzumab in subjects with CLL/SLL, lymphocytosis was infrequent (7% with ibrutinib + BR versus 6% with placebo + BR and 7% with ibrutinib + obinutuzumab versus 1% with chlorambucil + obinutuzumab).

Lymphocytosis was not observed in subjects with WM treated with ibrutinib.

1.4.2.11. Interstitial Lung Disease

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines as needed (see Section 5.3.1.4).

1.4.2.12. Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.4.2.13. Long-term Safety

The long-term safety data over 4 years from 1,177 subjects (CLL/SLL n = 807 and MCL n = 370) treated with ibrutinib were analyzed. The median duration of treatment for CLL/SLL was 45 months with 70% and 40% of subjects receiving treatment for more than 2 years and 4 years. The median duration of treatment for MCL was 11 months with 31% and 14% of subjects receiving treatment for more than 2 years and 4 years. The overall known safety profile of ibrutinib-exposed subjects remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater

hypertension was 4% (year 0-1), 6% (year 1-2), and 8% (year 3 – 4). The incidence for the 4-year period was 10%.

1.5. Study Rationale

In summary, the poor outcomes for patients with relapsed and refractory B-ALL and the clinical efficacy and mechanisms of action of ibrutinib and blinatumomab strongly support the study of these two drugs in combination for relapsed and refractory B-ALL (reviewed in Sections 1.1, 1.1.1, 1.1.2, and 1.3.1). Blinatumomab is FDA-approved for the treatment of relapsed and refractory B-ALL, but the efficacy of blinatumomab is significantly impaired in the presence of significant disease burden and inadequate numbers of cytotoxic T cells (12, 14, 15). Additionally, Blinatumomab has similar activity in both Ph+ and Ph- B-ALL (12, 13). BTK signaling has been shown to play a role in the pathogenesis of B-ALL and inhibition of this pathway has been shown to have anti-B-ALL activity in pre-clinical models (22-26, 30). Additionally, ibrutinib inhibits ITK, which promotes Th1-based immune responses important for the efficacy of blinatumomab (31, 32). Furthermore, ibrutinib pre-treatment enhanced the Th1-based immune response to Listeria in a mouse model of CLL (31). Therefore, we hypothesize that the addition of ibrutinib to blinatumomab will lead to synergistic anti-B-ALL activity, both through the direct anti-B-ALL effect of ibrutinib as well as the immunomodulatory effect of ibrutinib. Furthermore, we hypothesize that initiation of ibrutinib one week prior to the initiation of blinatumomab will lead to direct anti-B-ALL activity, and perhaps more importantly, will prime the Th1-based immune response necessary for effective blinatumomab redirected CD19-positive cell lysis by cytotoxic T-cells. This synergistic activity could potentially overcome two of the currently identified major reasons for blinatumomab failure, elevated bone marrow blast count and low CD3-positive T cell numbers. We predict this synergy will lead to a meaningful improvement in CR rate and other endpoints such as overall response rate, RFS, OS, MRD response rate, and proportion of patients bridged to transplant. We predict that the combination of ibrutinib and blinatumomab will be safe and well tolerated. To test our hypotheses, we propose to study the combination of standard doses of blinatumomab with ibrutinib. We will use ibrutinib continuously dosed at 560mg daily based on prior studies (NCT02129062, Ibrutinib Package Insert and Ibrutinib IB), and will start ibrutinib one week prior to initiation of blinatumomab (31). Because of the mechanisms of ibrutinib and blinatumomab metabolism, there are no predicted drug-drug interactions, and formal pharmacokinetic testing is therefore not planned. The planned study dose levels are the FDA-labeled doses and schedules with known toxicity profiles at these doses, and testing of multiple dose levels is not planned. Because there is potential for non-predicted overlapping or novel toxicities, this study will include a safety lead-in phase. We will perform a safety lead-in on the first 6-9 subjects, and we will use a Simon's two-stage design to minimize the number of patients required to detect a clinically meaningful improvement in CR rate for the combination compared to blinatumomab alone. Success of this study could have a significant impact in the care of relapsed and refractory B-ALL patients; pioneer the combination of immunomodulatory drugs with blinatumomab; and could lead to a larger randomized phase 2 or 3 study comparing blinatumomab with ibrutinib plus blinatumomab.

2. STUDY OBJECTIVE

2.1. Primary Objective/Endpoints

The primary objective is to evaluate the efficacy of ibrutinib and blinatumomab in patients with relapsed or refractory B-ALL as measured by complete response (CR) rate.

2.2. Secondary Objective(s)/Endpoints

Secondary objective: The secondary objective is to further examine the efficacy and safety of ibrutinib and blinatumomab in patients with relapsed or refractory B-ALL as measured by overall response rate (ORR, defined as CR plus CR with incomplete count recovery [CRi], or CR plus CR with partial hematologic recovery [CRh]), relapse free survival (RFS), overall survival (OS), minimal residual disease (MRD) response, proportion of patients bridged to allogeneic hematopoietic cell transplant (allo-HCT), and toxicity.

2.3. Exploratory Objective(s)/Endpoints

Exploratory objective: The exploratory objectives are to examine the pharmacodynamic effects of ibrutinib and blinatumomab in patients with relapsed or refractory B-ALL as measured by BTK and ITK expression and occupancy analysis and immune correlative analysis (including plasma cytokines, flow cytometric analysis of T cell subsets and NK cells, and T cell functional assays).

3. STUDY DESIGN

3.1. Overview of Study Design

This is a non-randomized open-label prospective phase 2 study of the combination of ibrutinib with blinatumomab in subjects with relapsed or refractory B-ALL. The study will consist of two parts. In the first part, a safety lead-in cohort will test ibrutinib 560mg in combination with blinatumomab in the first 6-9 patients. In the second part, up to 18 subjects (including subjects in safety lead-in cohort) will be treated using a Simon's minimax two-stage design (34).

Treatment Regimen: the first two cycles will be considered induction therapy. Subjects achieving a CR/CRi during induction will be able to receive up to three additional cycles of consolidation, for a total of five cycles. Treatment with ibrutinib will continue until either disease progression OR withdrawal of informed consent OR unacceptable or intolerable toxicities. Blinatumomab dosing is per standard of care (also see Blinatumomab package insert) (12).

Cycle 1 (49 days):
Ibrutinib 560mg PO daily days 1-49

Blinatumomab 9mcg/day CIV days 8-14
Blinatumomab 28mcg/day CIV days 15-35

Cycles 2-5 (42 days/cycle):
Ibrutinib 560mg PO daily days 1-42
Blinatumomab 28mcg/day CIV days 1-28

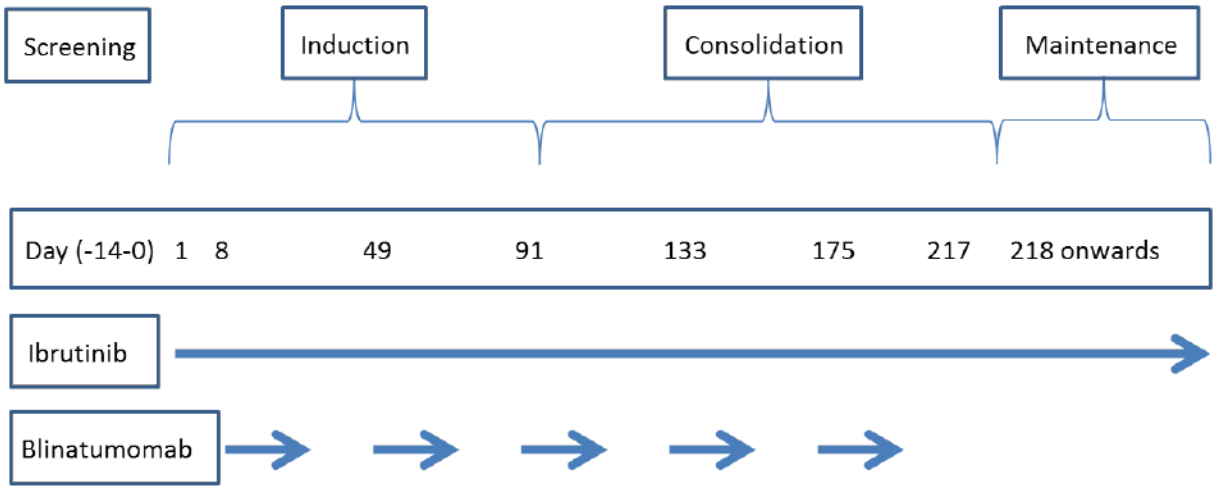
Maintenance Ibrutinib (28 days/cycle):
Ibrutinib 560mg PO daily days 1-28

Number of Cycles: subjects will receive up to 5 total cycles of therapy. Subjects will receive up to 2 cycles of induction unless they develop disease progression, treatment intolerance, or withdraw informed consent at which point they will be removed from protocol. Subjects in CR/CRi after induction (cycles 1-2) will receive up to 3 cycles of consolidation unless they demonstrate disease progression, treatment intolerance, or withdraw informed consent at which point they will be removed from protocol. Treatment with ibrutinib will continue until either disease progression OR physician/patient choice OR unacceptable or intolerable toxicities.

Duration of Follow-up: follow-up for safety monitoring after completion of therapy for up to 6 months until relapse, disease progression, initiation of a new treatment or up to 6 months, whichever occurs first.

The study schema is shown in Figure 3-1.

Figure 3-1. Study Schema



3.2. Study Design Rationale

This is a non-randomized open-label prospective phase 2 study to test the efficacy and safety of the combination of ibrutinib with blinatumomab in subjects with relapsed or refractory B-ALL. The poor outcomes for patients with relapsed and refractory B-ALL and the clinical efficacy and

mechanisms of action of ibrutinib and blinatumomab strongly support the study of these two drugs in combination for relapsed and refractory B-ALL (reviewed in Sections 1.1, 1.3, and 1.5).

Ibrutinib will be added to the standard blinatumomab backbone as established by Topp et al (12). Based on preclinical data, ibrutinib will be started one week prior to initiation of blinatumomab (31). The dose of ibrutinib will be 560mg PO daily, as established by prior studies (NCT02129062, Ibrutinib Package Insert and Ibrutinib IB), and the dose of blinatumomab will be as per the Blinatumomab Package Insert. Because ibrutinib and blinatumomab have not been tested before in combination, the study will start with a safety lead-in phase with 6-9 patients evaluated for dose-limiting toxicities. If less than 3 DLTs occur during the safety lead-in phase, accrual will continue up to a total of 18 subjects (including subjects in safety lead-in cohort) using a Simon's minimax two-stage design to determine the sample size. The primary endpoint will be rate of CR after two cycles of treatment (induction phase). The sample size is predicted to be sufficient to test our hypothesis that that the addition of ibrutinib to blinatumomab will lead to synergistic anti-B-ALL activity, both through the direct anti-B-ALL effect of ibrutinib as well as the immunomodulatory effect of ibrutinib.

There are no predicted significant drug-drug interactions with the combination of ibrutinib and blinatumomab. Ibrutinib is metabolized by CYP3A and is excreted by the liver. Blinatumomab metabolism has not been fully characterized, but like other protein therapeutics, it is expected to be degraded into small peptides and amino acids via catabolic pathways (see Blinatumomab Package Insert). Therefore, we do not plan to test pharmacokinetics in this study.

3.2.1. Study Population and Treatment

This study will enroll adult subjects with a confirmed diagnosis of relapsed or refractory B-ALL with measureable bone marrow lymphoblasts or biopsy-proven extramedullary site measurable by CT or PET/CT imaging. Ph+ B-ALL patients must have failed treatment with at least one second generation tyrosine kinase inhibitor (13). Subjects with B-ALL in remission with less than 5% blasts with minimal residual disease greater than or equal to 0.1% will also be enrolled. Prior allogeneic hematopoietic stem cell transplant (allo-HCT) is allowed. The study will be conducted at the University of California (UC) Davis Comprehensive Cancer Center and at University of Southern California (USC) Norris Comprehensive Cancer Center. The study may be expanded to other sites to meet protocol objectives.

Ibrutinib in combination with blinatumomab will be investigated. Ibrutinib dose will be 560mg daily, consistent with prior studies (NCT02129062, Ibrutinib Package Insert and Ibrutinib IB), and standard blinatumomab dosing will be used as per the blinatumomab package insert. Ibrutinib will be given continuously, starting one week prior to the start of blinatumomab and the two drugs will be given together for up to 5 total cycles in the absence of progression, intolerance, allo-HCT, withdrawal of informed consent, or any other reason as described in Section 9.

3.2.2. Dose Selection

The selected dose of ibrutinib is 560 mg 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 post dose at dose levels ≥2.5 mg/kg. A dose greater than 2.5 mg/kg was considered necessary to achieve consistent, full BTK occupancy, in previous PCYC studies. 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, including R-CHOP chemotherapy. The selected dose of blinatumomab is 9-28mcg/day CIV daily as per the standard of care for relapsed and refractory B-ALL (see Blinatumomab package insert).

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

23. Pathologically confirmed diagnosis of relapsed or refractory B-cell acute lymphoblastic leukemia/lymphoma with measurable bone marrow lymphoblasts or biopsy-proven extramedullary site measurable by CT or PET/CT imaging. Philadelphia chromosome-positive (Ph+) B-ALL patients must have failed treatment with at least one second generation tyrosine kinase inhibitor. Subjects with B-ALL in remission with less than 5% blasts, with or without count recovery, but with minimal residual disease (MRD) greater than or equal to 0.1% are eligible. Prior allo-HCT is allowed.

Laboratory

24. No Hematologic parameters for inclusion. Transfusion-dependent patients are eligible and platelet counts should be maintained greater than 10,000/mm3 throughout cycles 1 and 2.
25. Adequate hepatic and renal function defined as:
    a. Bilirubin less than or equal to 1.5 x upper limit of normal (ULN) (unless bilirubin rise is due to Gilbert's syndrome or B-ALL or non-hepatic origin).
    b. Serum aspartate transaminase (AST) or alanine transaminase (ALT) less than or equal to 3 x ULN (unless due to B-ALL)
    c. Estimated Creatinine Clearance greater than or equal to 30 ml/min (Cockcroft-Gault) or serum creatinine less than or equal to 2 x ULN.
26. PT/INR ≤1.5 x ULN and PTT (aPTT) ≤1.5 x ULN (unless B-ALL related).

Demographic

27. Men and women ≥ 18 years of age.
28. Karnofsky Performance Status (KPS) performance status of 60% or greater.

Ethical/Other

29. Ability to understand and willingness to sign an informed consent form.
30. Ability to adhere to the study visit schedule and other protocol requirements.
31. Female subjects who are of non-reproductive potential (i.e., 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 childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to the first study drug administration.
32. Male and female subjects who agree to use both a highly effective methods of birth control (e.g., condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[2], or sterilized partner) and a barrier method (e.g. condoms, vaginal ring, sponge, etc.) during the period of therapy and for 90 days after the last dose of study drug.
33. Eligibility of patients receiving any medications or substances known to affect or with the potential to affect the activity or pharmacokinetics of ibrutinib or blinatumomab will be determined following review of their case by the Investigator.

4.2. Exclusion Criteria

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

<u>Disease-Related</u>

1. Diagnosis of T-ALL or Burkitt's Leukemia/Lymphoma.
2. Patients with current evidence of active CNS leukemia.

<u>Concurrent Conditions</u>

3. History of treatment with ibrutinib or blinatumomab.
4. Investigational therapy, chemotherapy, immunotherapy, radiotherapy, or systemic GVHD therapy within two weeks or five half-lives (whichever is shorter). Steroids, hydroxyurea and/or leukapheresis are allowed to control blast count prior to the first dose of study drug.

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[2] 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

5. Prior allo-HCT less than three months from the time of enrollment.
6. Any active acute GVHD or chronic GVHD greater than Grade 1.
7. History of allergic reactions attributed to compounds of similar chemical or biologic composition to ibrutinib and blinatumomab or other agents used in this study.
8. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
9. Recent culture-documented infection requiring intravenous antimicrobials that was completed ≤7 days before the first dose of study drug or any uncontrolled active systemic infection. Fever of unknown origin is not an exclusion criterion, as this may be disease-related.
10. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, v4.03), Grade ≤2, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.
11. Known bleeding disorders (e.g., von Willebrand's disease) or hemophilia.
12. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
13. Active infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. Subjects with HIV must have a CD4 count at or above the institutional lower limit of normal and not taking prohibited CYP3A strong inhibitors.
14. Major surgery within 4 weeks of first dose of study drug.
15. Any life-threatening illness, medical condition, or organ system dysfunction, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, active autoimmune disorder, or psychiatric illness/social situations that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk. 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 enrollment.
16. History of other malignancies, except for malignancy surgically resected (or treated with other modalities) with curative intent, adequately treated in situ carcinoma of the breast or cervix uteri, basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin. Malignancy treated with curative intent with no known active disease present for ≥ 3 years.
17. Concomitant use of warfarin or other Vitamin K antagonists.
18. Subjects who received a strong cytochrome P 450 (CYP) 3A inhibitor within 7 days prior to the first dose of ibrutinib or subjects who require continuous treatment with a strong CYP3A inhibitor (see Appendix 3).
19. Subjects with chronic liver disease with hepatic impairment Child-Pugh class B or C (see Appendix 4)

20. Breastfeeding or pregnant.
21. Participation in clinical trials with other investigational agents not included in this trial throughout the duration of this trial.
22. Unwilling or unable to participate in all required study evaluations and procedures or 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 safety lead-in cohort. If fewer than 3 patients experience DLTs then the study will accrue up to 18 subjects as per the Simon's minimax two-stage design (see Section 10.3).

5.2. Study treatment

This will be a non-randomized open-label prospective phase 2 study of the combination of ibrutinib with blinatumomab in subjects with relapsed or refractory B-ALL.

5.2.1. Route and schedule

Study treatment is summarized in Section 3.1 and Figure 3-1. Ibrutinib in combination with blinatumomab will be tested in subjects with relapsed or refractory B-ALL.

Treatment Regimen: the first two cycles will be considered induction therapy. Subjects achieving a CR/CRi during induction will be able to receive up to three additional cycles of consolidation, for a total of five cycles. Treatment with ibrutinib will continue until either disease progression OR withdrawal of informed consent OR unacceptable or intolerable toxicities.

Cycle 1 (49 days):
Ibrutinib 560mg PO daily days 1-49
Blinatumomab 9mcg/day CIV days 8-14
Blinatumomab 28mcg/day CIV days 15-35

Cycles 2-5 (42 days/cycle):
Ibrutinib 560mg PO daily days 1-42
Blinatumomab 28mcg/day CIV days 1-28

Maintenance Ibrutinib (28 days/cycle):
Ibrutinib 560mg PO daily days 1-28

Cycle Length: 49 days for cycle 1 and 42 days for cycles 2-5 (unless cycle stopped early due to adverse events [see Section 5.3.2.5]. Maintenance cycles are 28 days long.

Number of Cycles: subjects will receive up to 5 total cycles of therapy. Subjects will receive up to 2 cycles of induction unless they develop disease progression, treatment intolerance, or withdraw informed consent at which point they will be removed from protocol. Subjects in CR/CRi after induction (cycles 1-2) will receive up to 3 cycles of consolidation unless they demonstrate disease progression, treatment intolerance, or withdraw informed consent at which point they will be removed from protocol. Treatment with ibrutinib will continue until either disease progression OR physician/patient choice OR unacceptable or intolerable toxicities.

Duration of Follow-up: follow-up for safety monitoring after completion of therapy for up to 6 months until relapse, disease progression, initiation of a new treatment or 6 months follow-up, whichever occurs first.

Duration of Study: maximum total study participation for a subject is 1.1 years (approximately 7 months of treatment and 6 months of follow-up).

5.2.2. Rules for the Safety Lead-In Cohort

The intended study dose of ibrutinib 560mg in combination with blinatumomab will be tested in the first 6 patients. For each subject in the safety lead-in cohort, the DLT assessment period will consist of the first cycle of study therapy (days 1-49). If 0-1 dose limiting toxicities (DLTs) are observed then the study will continue to accrue as per the Simon's two-stage design (Section 10.3). If 2 DLTs are observed in the first 6 patients, then 3 additional subjects will be assessed for DLTs. If 3 or more of the 9 subjects experience DLTs, enrollment will be halted at the 560mg dose level and an ibrutinib dose of 420mg will be considered. For the safety lead-in, if patients do not experience a DLT during cycle 1 but miss more than 25% of the total planned treatment doses for the cycle, they will be replaced.

5.2.3. Definitions of Dose-Limiting Toxicities (DLT)

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Effects (CTCAE) version 4.03 will be used. Toxicities will be considered related to the study drug unless there is a clear, well-documented, alternative explanation for the adverse effect.

DLT assessments will be based on treatment-related adverse events (AEs) in the first cycle (days 1-49). All patients who are not evaluable for toxicity will be replaced. Subjects will receive cycle 1 therapy regardless of neutropenia, anemia, or thrombocytopenia. RBC and platelet transfusion support is allowed during this time. Filgrastim will not be permitted during cycle 1, unless indicated for the treatment of febrile neutropenia. Dose limiting toxicity (DLT) in a given patient is defined as:

Hematologic:

Due to the nature of this disease, hematologic AEs will not be considering DLTs; however, prolonged myelosuppression in the presence of a hypocellular bone marrow (i.e. cellularity 5% or less without evidence of B-ALL) that lasts greater or equal to two weeks after the end of cycle 1 will be considered dose-limiting myelosuppression.

Non-Hematologic:

1. Any Grade 5 toxicity possibly related to study drug.

2. Any Grade 3 or higher non-hematologic event (per NCI CTCAE, v4.03) that occurs during the first treatment cycle (C1D1-C2D1 pre-dose) that does not reverse to grade 2 or lower prior to the start of cycle 2 or if any same Grade 3 or higher toxicity occurs upon resumption of the study treatment during Cycle 1 and is considered related to study treatment in the opinion of the investigator with the following modifications:

- Grade 3 infection or febrile neutropenia is not a DLT, however an infection with life-threatening consequences or requiring urgent intervention (Grade 4) will be considered a DLT if it is determined to be study drug related (e.g., in a subject starting treatment with a normal neutrophil count).
- Grade 3 nausea, vomiting, or diarrhea persisting less than or equal to 7 days.
- Grade 3 fatigue persisting less than or equal to 7 days
- Grade 3 AST or ALT elevation persisting for less than or equal to 7 days. Grade 4 lasting for any duration of time not attributable to disease progression will be considered a DLT.
- Grade 3 rash persisting for less than or equal to 7 days despite steroids, unless it is a serious form of rash such as Toxic Epidermal Necrolysis, Steven's Johnson Syndrome or other desquamating rash or associated with anaphylaxis. Note, for patients with Grade 1-2 rash, treatment will be continued and topical steroids administered. For Grade 3 rash, treatment will be held up to 7 days and oral prednisone 1mg/kg daily administered for up to 7 days. Treatment will be resumed upon resolution of the rash to less than Grade 3. If the rash remains Grade 3 despite treatment interruption and steroids or if the rash progresses to Grade 4, this will be considered a DLT and treatment will be discontinued.
- Alopecia.

3. Tumor lysis syndrome associated with other dose-limiting adverse medical events will be considered a DLT.

4. Grade 3 or higher central nervous system events or cytokine release syndrome will be considered a DLT.

5.3. Study Medication

5.3.1. Ibrutinib

Please refer to the package insert at http://www.imbruvica.com for more details.

5.3.1.1. Formulation/Packaging/Storage

Ibrutinib capsules are provided as a hard gelatin capsule containing 70 mg or 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure 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 drug will be dispensed in child-resistant packaging.

Refer to the pharmacy manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

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

5.3.1.2. Dose and Administration

Ibrutinib 560 mg (4 x 140-mg capsules) should be administered orally once daily with a glass of water at approximately the same time each day. The capsules should be swallowed whole with water; the capsules should not be opened, broken, or chewed. Ibrutinib must not be taken with grapefruit juice. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Refer to Section 6.2 and Appendix 3).

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 or hospital on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated at each visit. Returned capsules must not be re-dispensed to anyone.

5.3.1.3. Overdose

There are limited data on the effects of ibrutinib overdose. 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). In a separate study, 1 healthy subject who received a dose of 1,680 mg experienced reversible Grade 4 hepatic enzyme increases (AST and ALT). 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.

5.3.1.4. Dose Modification for Adverse Reactions

Due to the nature of this disease, hematologic AEs will not be considering DLTs; however, prolonged myelosuppression in the presence of a hypocellular bone marrow (i.e., cellularity 5% or less without evidence of B-ALL) that lasts greater or equal to two weeks after the end of cycle 1 will be considered dose-limiting myelosuppression. Platelets should be maintained at a minimum level of 10,000/μL or higher. The dose of ibrutinib should be modified according to the dose modification guidelines in Table 5-1 (or Table 5-2 for selected cardiac adverse reactions) if any of the following toxicities occur:

- Grade 4 absolute neutrophil count (ANC) (<500/μL) for more than 7 days in patients starting a cycle with a normal (Grade 0) ANC.
- Grade 3 thrombocytopenia (25,000-<50,000/μL) with associated bleeding or grade 4 thrombocytopenia (<25,000/μL) in patients starting a cycle with a normal (Grade 0) platelet count.
- 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; or Grade 3 toxicity for which, in the opinion of the investigator, drug should be held.

Subjects requiring dose interruptions of more than four weeks will be removed from study.

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 anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (See Section 6.2.4).

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. The rationale for dose-escalation is that a higher dose of ibrutinib is predicted to more effectively target BTK and ITK and exert anti-B-ALL activity. Furthermore, adverse events may not be stereotypic in the same patient, as some toxicities might be more likely to occur in the setting of active disease as opposed to in the setting of complete remission.

Table 5-1. Ibrutinib Dose Modifications

Occurrence	Action to be Taken
First	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level (560 mg/day) or at 1 dose level lower (420 mg/day)
Second	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (420 mg/day or 280 mg/day if decreased with first occurrence)
Third	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (280 mg/day or 140 mg/day if decreased with second occurrence)
Fourth	Discontinue study drug

Interrupt ibrutinib therapy for the selected cardiac adverse reactions listed in Table 5-2 that are at least possibly related to ibrutinib, then follow the recommended dosage modifications once the adverse reaction has improved to Grade 1 or baseline (recovery). The dose modification recommendations in Table 5-2 supersedes the recommendations in Table 5-1 for grades 2 and 3 cardiac failure and cardiac arrhythmia events.

Table 5-2. Ibrutinib Dose Modifications for Selected Cardiac Adverse Reactions

Adverse Reaction[a,b]	Occurrence	Dose Modification for Starting Dose = 560 mg	Dose Modification for Starting Dose = 420 mg
Grade 2 cardiac failure	First	Restart at 420 mg daily[c]	Restart at 280 mg daily[c]
	Second	Restart at 280 mg daily[c]	Restart at 140 mg daily[c]
	Third	Discontinue ibrutinib	Discontinue ibrutinib
Grade 3 cardiac arrhythmias	First	Restart at 420 mg daily[c]	Restart at 280 mg daily[c]
	Second	Discontinue ibrutinib	Discontinue ibrutinib
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue ibrutinib	Discontinue ibrutinib

[a] See *Warnings and Precautions* in the current ibrutinib packet insert
[b] Grading based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria, or International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for hematologic toxicities in CLL/SLL.
[c] Evaluate the benefit-risk before resuming treatment.

5.3.1.5. Dose Modification for Hepatic Impaired Subjects

Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines Section 5.3.1.4. Ibrutinib is metabolized in the liver. In the population PK analysis (1,202 subjects), 179 subjects (14.9%)

had mild hepatic impairment according to National Cancer Institute criteria and 12 subjects (1.0%) had moderate hepatic impairment. These subjects did not show a significantly higher ibrutinib exposure compared with subjects with normal hepatic function. Subjects with clinically significant chronic liver disease with hepatic impairment at the time of screening (Child-Pugh class C) are excluded from study participation. Note, the Child-Pugh class does not apply for study eligibility purposes or dose modification purposes for patients without a history of chronic liver disease or for whom the abnormal lab values (e.g., bilirubin, albumin and INR) are related to the B-ALL/LBL. Concomitant use of strong CYP inhibitors is not permitted in subjects with chronic hepatic impairment. Refer to Appendix 4 for Child-Pugh classification for patients with chronic liver disease. Subjects with existing chronic liver disease at baseline or who develop chronic liver disease while on study should dose reduce or hold based on the Child-Pugh class (please refer to Table 5-3).

Table 5-3. Dose Modification Guidance for Subjects with Existing Hepatic Impairment at Baseline or Who Develop Chronic Liver Disease While on Study

	Child-Pugh class A (Mild hepatic impairment)		**Child-Pugh Class B (Moderate hepatic impairment)**		**Child-Pugh Class C (Severe hepatic impairment)**
	Ongoing at time of enrollment	Develops during study	Ongoing at time of enrollment	Develops during study	Develops during study
Ibrutinib Dose (daily)	140 mg	140 mg	70 mg	70 mg	Hold until improves to moderate [Class B] or better)

5.3.2. Blinatumomab

Please refer to the package insert at http://www.blincyto.com for more details. Blinatumomab (BLINCYTO) is commercially available and will be administered to study subjects per standard of care.

5.3.2.1. Summary of Clinical Safety for Blinatumomab

Please refer to the package insert at http://www.blincyto.com for complete details. The following is taken from the package insert.

The safety data described in this section reflect exposure to BLINCYTO in clinical trials in which 212 patients with relapsed or refractory ALL received up to 28 mcg/day. All patients received at least one dose of BLINCYTO. The median age of the study population was 37 years (range: 18 to 79 years), 63% were male, 79% were White, 3% were Asian, and 3% were Black or African American.

The most common adverse reactions (≥ 20%) were pyrexia (62%), headache (36%), peripheral edema (25%), febrile neutropenia (25%), nausea (25%), hypokalemia (23%), and constipation (20%).

Serious adverse reactions were reported in 65% of patients. The most common serious adverse reactions (≥ 2%) included febrile neutropenia, pyrexia, pneumonia, sepsis, neutropenia, device-related infection, tremor, encephalopathy, infection, overdose, confusion, *Staphylococcal* bacteremia, and headache.

Adverse reactions of Grade 3 or higher were reported in 80% of patients. Discontinuation of therapy due to adverse reactions occurred in 18% of patients treated with BLINCYTO. The adverse reactions reported most frequently as the reason for discontinuation of treatment included encephalopathy and sepsis. Fatal adverse events occurred in 15% of patients. The majority of these events were infections. No fatal adverse events occurred on treatment among patients in remission.

The adverse reactions with ≥ 10% incidence for any grade or ≥ 5% incidence for Grade 3 or higher are summarized below (n = 212).

Adverse Reaction	Any Grade[1] (%)	Grade 3 or Higher[1] (%)
Blood and lymphatic system disorders		
Febrile neutropenia	25	23
Anemia	18	13
Neutropenia	16	15
Thrombocytopenia	11	8
Leukopenia	9	8
Gastrointestinal disorders		
Nausea	25	0
Constipation	20	< 1
Diarrhea[2]	20	1
Abdominal pain	15	2
Vomiting	13	0
General disorders and administration site conditions		
Pyrexia	62	7
Peripheral edema	25	< 1
Fatigue	17	1
Chills	15	0
Chest pain	11	1
Immune system disorders		
Cytokine release syndrome	11	1
Infections and infestations		
Other pathogen infections	44	25
Bacterial infections	19	12
Fungal infections	15	7
Viral infections	13	4
Pneumonia	9	8
Sepsis	7	6
Investigations		
Increased alanine aminotransferase	12	6
Increased aspartate aminotransferase	11	4
Increased weight	11	0
Metabolism and nutrition disorders		
Hypokalemia	23	6
Hypomagnesemia	12	0
Hyperglycemia	11	7
Decreased appetite	10	3
Hypophosphatemia	6	5
Musculoskeletal and connective tissue disorders		
Back pain	14	2
Pain in extremity	12	1
Bone pain	11	3
Arthralgia	10	2
Nervous system disorders		
Headache	36	3
Tremor[3]	20	1
Dizziness	14	< 1

Adverse Reaction	Any Grade[1] (%)	Grade 3 or Higher[1] (%)
Psychiatric disorders		
Insomnia	15	0
Respiratory, thoracic, and mediastinal disorders		
Cough	19	0
Dyspnea[4]	15	5
Skin and subcutaneous tissue disorders		
Rash[5]	21	2
Vascular disorders		
Hypotension	11	2
Hypertension	8	5

[1] Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
[2] Diarrhea includes the following terms: colitis, diarrhea, enteritis, and neutropenic colitis.
[3] Tremor includes the following terms: resting tremor and tremor.
[4] Dyspnea includes the following terms: acute respiratory failure, bronchial hyperactivity, bronchospasm, dyspnea, dyspnea exertional, respiratory distress, respiratory failure, and wheezing.
[5] Rash includes the following terms: erythema, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, papular rash, and vesicular rash.

Additional important adverse reactions that did not meet the threshold criteria for inclusion above were:

Blood and lymphatic system disorders: leukocytosis (2%), lymphopenia (1%)

Cardiac disorders: tachycardia (8%)

General disorders and administration site conditions: edema (5%)

Immune system disorders: cytokine storm (1%)

Investigations: decreased immunoglobulins (9%), increased blood bilirubin (8%), increased gammaglutamyl-transferase (6%), increased liver enzymes (1%)

Metabolism and nutrition disorders: tumor lysis syndrome (4%), hypoalbuminemia (4%)

Nervous system disorders: encephalopathy (5%), paresthesia (5%), aphasia (4%), convulsion (2%), memory impairment (2%), cognitive disorder (1%), speech disorder (< 1%)

Psychiatric disorders: confusion (7%), disorientation (3%)

Vascular disorders: capillary leak syndrome (< 1%).

Hypersensitivity reactions related to BLINCYTO treatment were hypersensitivity (1%) and bronchospasm (< 1%).

5.3.2.2. Formulation/Packaging/Storage

BLINCYTO (blinatumomab) is a bispecific CD19-directed CD3 T-cell engager that binds to CD19 (expressed on cells of B-lineage origin) and CD3 (expressed on T cells). BLINCYTO is produced in Chinese hamster ovary cells. It consists of 504 amino acids and has a molecular weight of approximately 54 kilodaltons.

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager that binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B cells. Blinatumomab mediates the formation of a synapse between the T cell and the tumor cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, which result in redirected lysis of CD19+ cells.

Please refer to the package insert at http://www.blincyto.com for more details on the clinical pharmacology of Blinatumomab.

Each BLINCYTO package contains 1 vial BLINCYTO and 1 vial IV Solution Stabilizer. BLINCYTO is supplied in a single-use vial as a sterile, preservative-free, white to off-white lyophilized powder for intravenous administration. Each single-use vial of BLINCYTO contains 35 mcg blinatumomab, citric acid monohydrate (3.35 mg), lysine hydrochloride (23.23 mg), polysorbate 80 (0.64 mg), trehalose dihydrate (95.5 mg), and sodium hydroxide to adjust pH to 7.0. After reconstitution with 3 mL of preservative-free Sterile Water for Injection, USP, the resulting concentration is 12.5 mcg/mL blinatumomab.

IV Solution Stabilizer is supplied in a single-use vial as a sterile, preservative-free, colorless to slightly yellow, clear solution. Each single-use vial of IV Solution Stabilizer contains citric acid monohydrate (52.5 mg), lysine hydrochloride (2283.8 mg), polysorbate 80 (10 mg), sodium hydroxide to adjust pH to 7.0, and water for injection.

How Supplied

Each BLINCYTO package (NDC 55513-160-01) contains:

One BLINCYTO 35 mcg single-use vial containing a sterile, preservative-free, white to off-white lyophilized powder

One IV Solution Stabilizer 10 mL single-use glass vial containing a sterile, preservative-free, colorless to slightly yellow, clear solution. Do not use the IV Solution Stabilizer to reconstitute BLINCYTO.

Storage and Handling

Store BLINCYTO and IV Solution Stabilizer vials in the original package refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light until time of use. Do not freeze.

Store and transport the prepared IV bag containing BLINCYTO solution for infusion at 2°C to 8°C (36°F to 46°F) conditions. Ship in packaging that has been validated to maintain temperature of the contents at 2°C to 8°C (36°F to 46°F). Do not freeze.

5.3.2.3. Dose and Administration

Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended. For the treatment of MRD-positive B-ALL patients, dosing and hospitalization recommendations can be adjusted to follow the blinatumomab package insert instructions for MRD-positive B-ALL patients per investigator discretion and in consultation with the study chair.

Do not flush the BLINCYTO infusion line especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications thereof. Preparation and administration errors resulting in overdose have occurred.

For complete details on drug preparation, administration, storage conditions, clinical pharmacology, and known precautions and adverse reactions, please see the prescribing information.

<u>Dosage</u>

- A single cycle of treatment of BLINCYTO consists of 4 weeks of continuous intravenous infusion followed by a 2-week treatment-free interval.
- For patients at least 45 kg in weight:
    - In Cycle 1, administer BLINCYTO at 9 mcg/day on Days 8–14 and at 28 mcg/day on Days 15–35.
    - For subsequent cycles, administer BLINCYTO at 28 mcg/day on Days 1–28.
- For patients less than 45 kg, refer to the prescribing information.
- Allow for at least 2 weeks treatment-free between cycles of BLINCYTO.
- A treatment course consists of up to 2 cycles of BLINCYTO for induction followed by 3 additional cycles for consolidation treatment (up to a total of 5 cycles).

<u>Special Considerations</u>

- Premedicate with dexamethasone 20 mg intravenously 1 hour prior to the first dose of BLINCYTO of each cycle, prior to a step dose (such as Cycle 1 day 8), or when restarting an infusion after an interruption of 4 or more hours.
- Administer BLINCYTO as a continuous intravenous infusion at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm.
- BLINCYTO infusion bags should be infused over 24 hours (preservative-free), 48 hours (preservative-free), or 7 days (with preservative; bacteriostatic water containing 0.9% benzyl alcohol). Infuse BLINCYTO solution according to the instructions on the pharmacy label on the bag at one of the following constant infusion rates:
    - Infusion rate of 10 mL/h for a duration of 24 hours, OR
    - Infusion rate of 5 mL/h for a duration of 48 hours, OR

  - Infusion rate of 0.6 mL/h for a duration of 7 days (Note: the 7-day infusion is not recommended for patients weighing less than 22 kg.)
- The BLINCYTO solution for infusion must be administered using polyolefin, PVC DEHP-free, or EVA IV tubing that contains a sterile, non-pyrogenic, low protein-binding, 0.2 micron in-line filter.
- Important Note: Do not flush the infusion line, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage. BLINCYTO should be infused through a dedicated lumen.

At the end of the infusion, any unused BLINCYTO solution in the IV bag and IV lines should be disposed of in accordance with local requirements.

Incompatibility Information

BLINCYTO is incompatible with di-ethylhexylphthalate (DEHP) due to the possibility of particle formation, which can lead to a cloudy solution.

- Use polyolefin, PVC DEHP-free, or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Use polyolefin, PVC DEHP-free, or EVA IV tubing sets.

Reconstitution and Preparation of Solution for Infusion

It is very important that the instructions for preparation (including admixing) and administration provided in this section are strictly followed to minimize medication errors (including underdose and overdose). Call 1-800-77-AMGEN (1-800-772-6436) if you have questions about the reconstitution and preparation of BLINCYTO.

Gather Supplies

NOTE: 1 package BLINCYTO includes 1 vial of BLINCYTO and 1 vial of IV Solution Stabilizer.

Before preparation, ensure you have the following supplies ready:

- 1 package of BLINCYTO for preparation of the following:
  - 9 mcg/day dose; preparation infused over 24 hours at a rate of 10 mL/h
  - 9 mcg/day dose; preparation infused over 48 hours at a rate of 5 mL/h
  - 28 mcg/day dose; preparation infused over 24 hours at a rate of 10 mL/h
- 2 packages of BLINCYTO for preparation of 28 mcg/day dose; preparation infused over 48 hours at a rate of 5 mL/h
- 6 packages of BLINCYTO for preparation of 28 mcg/day dose; preparation infused over 7 days at a rate of 0.6 mL/h.

The following supplies are also required, but not included in the package:

- Sterile, single-use disposable syringes
- 21- to 23- gauge needle(s) (recommended)
- Preservative-free Sterile Water for Injection, USP

- Sterile, non-pyrogenic, low protein-binding polyolefin, PVC non-DEHP, or EVA IV tubing with 0.2 micron in-line filter
    - Ensure that the IV tubing is compatible with the infusion pump.
- For 24- and 48-hour bag: 250 mL 0.9% Sodium Chloride IV bag
    - To minimize the number of aseptic transfers, it is recommended to use a 250 mL-prefilled IV bag. 250 mL-prefilled IV bags typically contain overfill with a total volume of 265 to 275 mL. BLINCYTO dose preparationpreparation instructions provided belowbelow are based on a starting volume of 265 mL to 275 mL 0.9% Sodium Chloride.
    - Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- For 7-day bag:
    - Empty IV bag
    - 90 mL bacteriostatic 0.9% NaCl, USP
    - 0.9% NaCl Injection, USP quantity sufficient (QS) to make a total volume of 110 mL bag

Aseptic Preparation

Aseptic technique must be strictly observed when preparing the solution for infusion since BLINCYTO vials do not contain antimicrobial preservatives. To prevent accidental contamination, prepare BLINCYTO according to aseptic standards, including but not limited to:

- Preparation must be done in a USP <797> compliant facility.
- Preparation must be done in an ISO Class 5 laminar flow hood or better.
- The admixing area should have appropriate environmental specifications, confirmed by periodic monitoring.
- Personnel should be appropriately trained in aseptic manipulations and admixing of oncology drugs.
- Personnel should wear appropriate protective clothing and gloves.
- Gloves and surfaces should be disinfected.

Special Considerations to Support Accurate Preparation

- IV Solution Stabilizer is provided with the BLINCYTO package and is used to coat the prefilled IV bag prior to addition of reconstituted BLINCYTO to prevent adhesion of BLINCYTO to IV bags and IV lines. Therefore, add IV Solution Stabilizer to the IV bag containing 0.9% Sodium Chloride. Do not use IV Solution Stabilizer for reconstitution of BLINCYTO.
- The entire volume of the admixed BLINCYTO will be more than the volume administered to the patient to account for the priming of the IV line and to ensure that the patient will receive the full dose of BLINCYTO.
- When preparing an IV bag, remove air from IV bag. This is particularly important for use with an ambulatory infusion pump.
- Use the specific volumes described in the admixing instructions to minimize errors in calculation.

Preparation of BLINCYTO Solution for Infusion Using a Prefilled 250 mL 0.9% Sodium Chloride IV Bag (24 hour and 48 hour preparations only)

Specific admixing instructions are provided for each dose and infusion time. Verify the prescribed dose and infusion time of BLINCYTO and identify the appropriate dosing preparation section listed below. Follow the steps for reconstituting BLINCYTO and preparing the IV bag.

Preparation of BLINCYTO 9 mcg/day infused over 24 hours at a rate of 10 mL/h

1. Use a prefilled 250 mL 0.9% Sodium Chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% Sodium Chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.5 mL of IV Solution Stabilizer to the IV bag with 0.9% Sodium Chloride. Gently mix the contents of the bag to avoid foaming. Discard remaining IV Solution Stabilizer vial.
3. Using a 5 mL syringe, reconstitute one vial of BLINCYTO using 3 mL of preservative-free Sterile Water for Injection, USP. Direct preservative-free Sterile Water for Injection, USP, toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. Do not shake.
    a. Do not reconstitute BLINCYTO with IV Solution Stabilizer.
    b. The addition of preservative-free Sterile Water for Injection, USP, to the lyophilized powder results in a final BLINCYTO concentration of 12.5 mcg/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colorless to slightly yellow. Do not use if solution is cloudy or has precipitated.
5. Using a 1 mL syringe, aseptically transfer 0.83 mL of reconstituted BLINCYTO into the IV bag. Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and prime the IV line only with the prepared solution for infusion.
8. Do not prime with 0.9% Sodium Chloride.
9. Store at 2°C to 8°C if not used immediately.

Preparation of BLINCYTO 9 mcg/day infused over 48 hours at a rate of 5 mL/h

1. Use a prefilled 250 mL 0.9% Sodium Chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% Sodium Chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.5 mL of IV Solution Stabilizer to the IV bag with 0.9% Sodium Chloride. Gently mix the contents of the bag to avoid foaming. Discard remaining IV Solution Stabilizer vial.
3. Using a 5 mL syringe, reconstitute one vial of BLINCYTO using 3 mL of preservative-free Sterile Water for Injection, USP. Direct preservative-free Sterile Water for Injection,

USP, toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. Do not shake.
   a. Do not reconstitute BLINCYTO with IV Solution Stabilizer.
   b. The addition of preservative-free Sterile Water for Injection, USP, to the lyophilized powder results in a final BLINCYTO concentration of 12.5 mcg/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colorless to slightly yellow. Do not use if solution is cloudy or has precipitated.
5. Using a 3 mL syringe, aseptically transfer 1.7 mL of reconstituted BLINCYTO into the IV bag. Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and prime the IV line only with the prepared solution for infusion. Do not prime with 0.9% Sodium Chloride.
8. Store at 2°C to 8°C if not used immediately.

Preparation of BLINCYTO 28 mcg/day infused over 24 hours at a rate of 10 mL/h

1. Use a prefilled 250 mL 0.9% Sodium Chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% Sodium Chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.6 mL of IV Solution Stabilizer to the IV bag with
3. 0.9% Sodium Chloride. Gently mix the contents of the bag to avoid foaming. Discard remaining IV Solution Stabilizer vial.
4. Using a 5 mL syringe, reconstitute one vial of BLINCYTO using 3 mL of preservative-free Sterile Water for Injection, USP. Direct preservative-free Sterile Water for Injection, USP, toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. Do not shake.
   a. Do not reconstitute BLINCYTO with IV Solution Stabilizer.
   b. The addition of preservative-free Sterile Water for Injection, USP, to the lyophilized powder results in a final BLINCYTO concentration of 12.5 mcg/mL.
5. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colorless to slightly yellow. Do not use if solution is cloudy or has precipitated.
6. Using a 3 mL syringe, aseptically transfer 2.6 mL of reconstituted BLINCYTO into the IV bag. Gently mix the contents of the bag to avoid foaming.
7. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
8. Remove air from the IV bag and prime the IV line only with the prepared solution for infusion. Do not prime with 0.9% Sodium Chloride.
9. Store at 2°C to 8°C if not used immediately.

Preparation of BLINCYTO 28 mcg/day infused over 48 hours at a rate of 5 mL/h

1. Use a prefilled 250 mL 0.9% Sodium Chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% Sodium Chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.6 mL of IV Solution Stabilizer to the IV bag with 0.9% Sodium Chloride. Gently mix the contents of the bag to avoid foaming. Discard remaining IV Solution Stabilizer vials.
3. Use two vials of BLINCYTO. Using a 5 mL syringe, reconstitute each vial of BLINCYTO using 3 mL of preservative-free Sterile Water for Injection, USP. Direct preservative-free Sterile Water for Injection, USP, toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. Do not shake.
    a. Do not reconstitute BLINCYTO with IV Solution Stabilizer.
    b. The addition of preservative-free Sterile Water for Injection, USP, to the lyophilized powder results in a final BLINCYTO concentration of 12.5 mcg/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colorless to slightly yellow. Do not use if solution is cloudy or has precipitated.
5. Using a 3 mL syringe, aseptically transfer 5.2 mL of reconstituted BLINCYTO into the IV bag (2.7 mL from one vial and the remaining 2.5 mL from the second vial). Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and prime the IV line only with the prepared solution for infusion. Do not prime with 0.9% Sodium Chloride.
8. Store at 2°C to 8°C if not used immediately.

Preparation of BLINCYTO 28 mcg/day infused over 7 days at a rate of 0.6 mL/h

1. Aseptically add 90 mL Bacteriostatic 0.9% Sodium Chloride, USP to the empty IV bag. Incompatibilities between blinatumomab and the empty IV bag must be observed. See **Incompatibility Information section above.**
2. Aseptically transfer 2.2 mL IV Solution Stabilizer to the IV bag containing the saline solution. Gently mix the contents of the bag to avoid foaming. Discard the vial containing the unused IV Solution Stabilizer.
3. Use 6 packages of blinatumomab. Using a 5 mL syringe, reconstitute each vial of BLINCYTO using 3 mL of preservative-free Sterile Water for Injection, USP. Direct preservative-free Sterile Water for Injection, USP, toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. Do not shake resulting concentration.
4. Aseptically transfer 16.8 mL of reconstituted BLINCYTO into the IV bag containing the saline solution and IV Solution Stabilizer. Gently mix the contents of the bag to avoid foaming.
5. Aseptically add 0.9% Sodium Chloride Injection, USP to QS the IV bag to a final volume of 110 mL, resulting in 0.74% benzyl alcohol. Gently mix the contents of the bag to avoid

foaming. The volume of 0.9% Sodium Chloride Injection, USP needed to QS to final volume of 100 mL is 1 mL.

6. Under aseptic conditions, attach the IV tubing to the IV bag. An in-line filter is not required for a 7-day bag.
    a. Ensure that the IV tubing is compatible with the infusion pump and BLINCYTO.
7. Remove air from the IV bag. This is particularly important for use with an ambulatory infusion pump. Prime the IV tubing only with the prepared solution for infusion. Do not prime with 0.9% Sodium Chloride Injection, USP.
8. Store at 2°C to 8°C if not used immediately.

Storage Requirements

The information in Table 5-4 indicates the storage time for the reconstituted BLINCYTO vial and prepared IV bag containing BLINCYTO solution for infusion. Lyophilized BLINCYTO vial and IV Solution. Stabilizer may be stored for a maximum of 8 hours at room temperature.

Table 5-4. Storage Time for Reconstituted BLINCYTO and IV Solution Stabilizer

	Maximum Storage Time	
	Room Temperature 23°C to 27°C (73°F to 81°F)	Refrigerated 2°C to 8°C (36°F to 46°F)
Reconstituted BLINCYTO Vial	4 hours	24 hours
Prepared BLINCYTO Infusion Bag (*Preservative-Free*)	48 hours*	8 days
Prepared BLINCYTO Infusion Bag (*with Preservative*)	7 days*	14 days

* Storage time includes infusion time. If the prepared BLINCYTO infusion bag is not administered within the time frames and temperatures indicated, it must be discarded; it should not be refrigerated again.

Patient Care Implications: The effect of blinatumomab on fertility has not been evaluated. Blinatumomab is not recommended in pregnant women and in women of childbearing potential not using contraception. It is not known whether blinatumomab or its metabolites are excreted in human milk. Women are not allowed to breastfeed while receiving blinatumomab. Monitor patients for cytokine release syndrome, tumor lysis syndrome, and infusion reaction. Refer to protocol for specific recommendation. Monitor patients for psychiatric events such as confusion, disorientation, and cognitive attention disturbances. Patients should not drive or operate dangerous machinery while receiving blinatumomab.

5.3.2.4. Overdose

Overdoses have been observed, including one patient who received 133-fold the recommended therapeutic dose of BLINCYTO delivered over a short duration. Overdoses resulted in adverse reactions which were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, interrupt the infusion, monitor the patient for signs of toxicity, and provide supportive care. Consider reinitiation of

BLINCYTO at the correct therapeutic dose when all toxicities have resolved and no earlier than 12 hours after interruption of the infusion.

5.3.2.5. Warnings, Adverse Reactions, Drug-Drug Interactions and Use in Specific Populations

Please refer to the package insert at http://www.blincyto.com for more details.

5.3.2.6. Dose Modification for Adverse Reactions

If the interruption after an adverse event related to blinatumomab is no longer than 7 days, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse event is longer than 7 days, start a new cycle. Cycles in which the blinatumomab is held can be extended to allow for the intended 14-day break between cycles for the blinatumomab. In those situations, the ibrutinib can be continued since ibrutinib is given in a continuous fashion. For example, if blinatumomab is held for 5 days in cycle 2 and the 28th and final day of blinatumomab infusion for that cycle therefore falls on cycle 2, day 33, then the total length of cycle 2 would be extended by 5 days to 47 days with ibrutinib continuously administered throughout, to accommodate the 14-day break between the end of cycle 2 blinatumomab and the start of cycle 3 blinatumomab. Alternatively, cycles 2-5 have a 3-day window for day 1 (see Appendix 1), so if the blinatumomab hold is 3 days or less, the start of the next cycle could be delayed and ibrutinib held for up to 3 days.

Table 5-5. Blinatumomab Dose Modifications

Toxicity	Grade[1]	Action[2]
Cytokine Release Syndrome (CRS)	Grade 3 -	Withhold BLINCYTO until resolved, then restart BLINCYTO at 9mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.
	Grade 4 -	Discontinue BLINCYTO permanently
Neurological Toxicity	Seizure -	Discontinue BLINCYTO permanently if more than one seizure occurs
	Grade 3 -	Withhold BLINCYTO until no more than Grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently.
	Grade 4 -	Discontinue BLINCYTO permanently.
Other Clinically Relevant Adverse Reactions[3]	Grade 3 -	Withhold BLINCYTO until no more than Grade 1 (mild), then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently.
	Grade 4 -	Consider discontinuing BLINCYTO permanently.

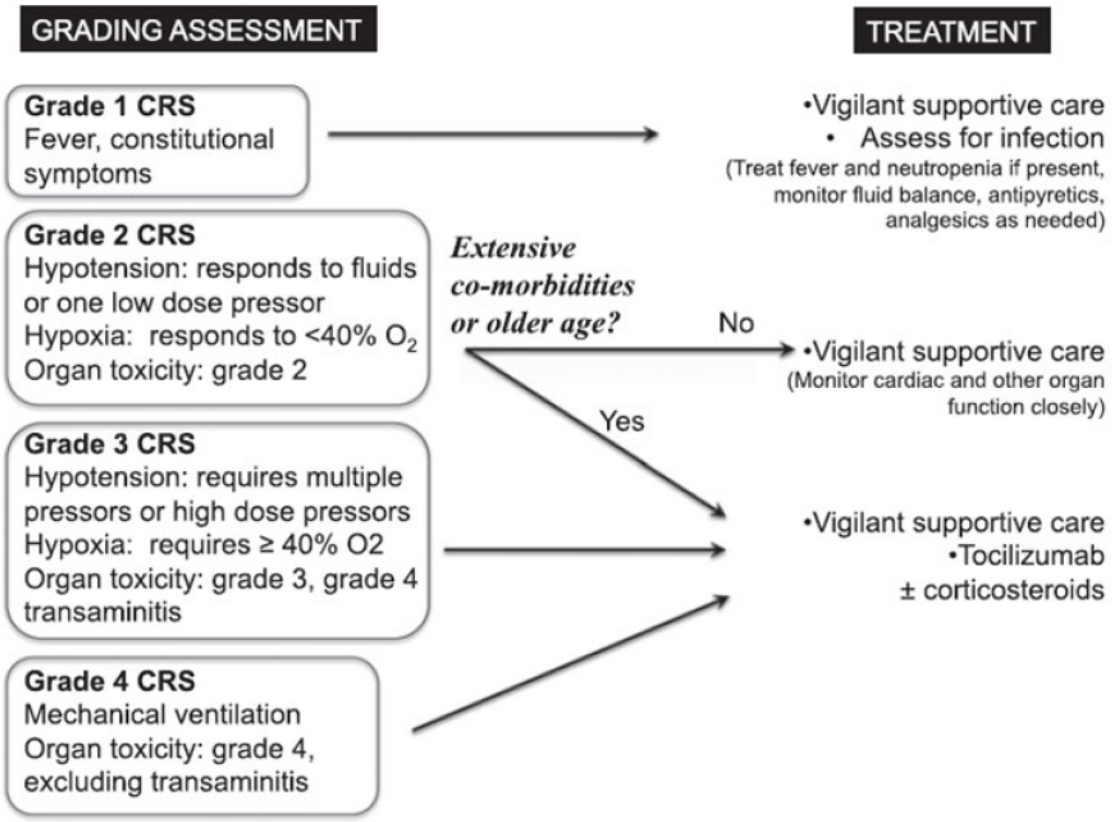
Ref: Blincyto Package Insert (www.blincyto.com).

1. Based on the Common Terminology Criteria for Adverse Events (CTCAE). Grade 3 is severe, and Grade 4 is life-threatening.
2. When blinatumomab is withheld due to toxicity for more than 4 hours Dexamethasone 20 mg should be considered when resuming the blinatumomab and at the time of escalation.
3. Other clinically relevant adverse reactions should be at least possibly related to blinatumomab or clinically relevant and necessitating drug hold in the opinion of the investigator, and do not include hematologic AEs.

Additional dose modifications of blinatumomab are permitted at the Investigator's discretion for subjects in CR after cycles 1 or 2.

Cytokine release syndrome and neurotoxicity management (e.g., steroids and other interventions) is at the discretion of the investigator. Blinatumomab dose should be modified as per Table 5-5 above. A suggested management approach for cytokine release syndrome can be found in the review by Lee et al., Blood 2014 (35). For example, Lee et al. suggest:

Figure 5-1. Management of Cytokine Release Syndrome



5.4. Dose Modifications in the Setting of Combination Therapy

Some AEs may not be attributable specifically to ibrutinib or blinatumomab. In these instances, one or both of the study medications should be dose-modified according to Sections 5.3.1.4 and 5.3.2.5 at the Investigator's discretion. Study treatment should be discontinued in the event of a

toxicity lasting more than 28 days; however, the patient may remain on study with blinatumomab at the Investigator's discretion.

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 Sections 9.2 and 9.3.

An End-of-Treatment Visit (Section 8.3) is required for all subjects except for those subjects who have withdrawn full consent.

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. Use of neutrophil growth factors (filgrastim and pegfilgrastim [For Cycle 1 administration, please see section 5.2.3]) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines (36). Transfusions may be given in accordance with institutional policy.

Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 1mg/kg/day of prednisone or equivalent are permitted during study treatment.

The use of hydroxyurea (HU), steroids and/or leukapheresis during the screening phase is permitted to control the B-cell acute lymphoblastic leukemia/lymphoma until 1 day prior study treatment. Use of HU, steroids and/or leukapheresis after study treatment has started to control the B-cell acute lymphoblastic leukemia/lymphoma is at the discretion of the investigator in conjunction with the study chair.

Prophylactic intrathecal chemotherapy is allowed during periods off blinatumomab (e.g., during cycle 1 days 36-49, during cycles 2-5 days 29-42 or during maintenance) per investigator discretion.

6.2. Medications to be Used with Caution

6.2.1. CYP3A- Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4. Concomitant use of ibrutinib with drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure. Avoid grapefruit and Seville oranges during ibrutinib treatment as these contain moderate inhibitors of CYP3A. Dose adjustment of ibrutinib due to concomitant use of CYP3A inhibitors should follow Table 6-1.

Table 6-1. Dose Modification Guidance for CYP3A Inhibitors

Patient Population	Co-administered Drug	Recommended Ibrutinib Dosage
B-Cell Malignancies	• Moderate CYP3A inhibitor	280 mg once daily Modify dose as recommended (see section 5.3.1.4).
	• Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	280 mg once daily Modify dose as recommended (see section 5.3.1.4).
	• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole intravenously 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	70 mg once daily Interrupt dose as recommended (see section 5.3.1.4).
	• Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib.
Chronic Graft versus Host Disease	• Moderate CYP3A inhibitors	420 mg once daily Modify dose as recommended (see section 5.3.1.4).
	• Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	280 mg once daily Modify dose as recommended (see section 5.3.1.4).
	• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole intravenously 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	140 mg once daily Modify dose as recommended (see section 5.3.1.4).

Patient Population	Co-administered Drug	Recommended Ibrutinib Dosage
	• Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib.

After discontinuation of a CYP3A inhibitor, resume previous dose of inhibitors.

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

A list of common CYP3A inhibitors and inducers is provided in Appendix 3. 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), nor other major transporters, except OCT2. The dihydrodiol metabolite and other metabolites are P-gp substrates. Ibrutinib is a mild inhibitor of P-gp and breast cancer resistance protein (BCRP). 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 and BCRP after a therapeutic dose. There is no clinical data available. To minimize a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin or methotrexate, should be taken at least 6 hours before or after ibrutinib. Ibrutinib may also inhibit BCRP systemically and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

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

Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. Bleeding events of any grade, including bruising and petechiae, occurred in subjects treated with ibrutinib. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 6.4). Subjects with congenital bleeding diathesis have not been studied.

Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g., atrial fibrillation) should 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 and blinatumomab treatment. Prophylactic intrathecal chemotherapy is allowed during periods off blinatumomab (e.g., during cycle 1 days 36-49, during cycles 2-5 days 29-42 or during maintenance) per investigator discretion. Also, use of HU, steroids and/or leukapheresis after study treatment has started to control the B-cell acute lymphoblastic leukemia/lymphoma is at the discretion of the investigator in conjunction with the study chair. Refer as well to Section 6.1 and 6.2 for additional limitations to concurrent medications.

6.4. Guidelines for Ibrutinib Management with Surgeries or Procedure

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, skin or 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 for these procedures.

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 (except for emergency procedures) 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.

7. STUDY EVALUATIONS

7.1. Description of Procedures

A cycle has a duration of 42 days throughout this study, with the exception of cycle 1, which lasts 49 days.

All screening clinical and laboratory assessments must be performed within 14 days of Study Day 1 and prior to the first dose of study treatment.

7.1.1. Assessments

7.1.1.1. Informed Consent Form

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 (Section 4). In addition to the review of screening procedures and results, documentation of pathologic confirmation of eligible disease (Section 4) is required for confirmation of eligibility prior to enrollment.

7.1.1.3. Medical History and Demographics

The subject's complete 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 for 6 months or 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 Pharmacyclics or study sponsor.

7.1.1.5. Adverse Events

The accepted regulatory definition for an adverse event is provided in Section 11.1. All medical occurrences that meet the adverse event definition will be documented in the source documents from the time of first dose of study treatment until 30 days following the last dose of study drugs. SAEs will be reported to the Pharmacyclics and the study sponsor from the time of first dose of study treatment.

Both serious and non-serious AEs will be recorded in the CRF from the first dose of study drug until 30 days after the last dose of study drug(s).

Additional important requirements for adverse event and serious adverse event reporting are explained in Section 11.

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.

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. KPS

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).

The ECOG and KPS performance indices are provided in Appendix 2. A score of 60% (KPS) or greater 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 ≤30,000/µL at baseline or ≤20,000/µL during the first cycle will be required to have platelet assessment 2 times a week until such time that the nadir is >20,000/µL.

7.1.2.2. Chemistry (Serum)

Serum chemistry parameters will include 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.

7.1.2.3. Coagulation Studies

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

7.1.2.4. Hepatitis Serologies

Hepatitis serologies include Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B surface antibody, and Hepatitis B core antibody and 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 prior to enrollment of subjects who are Hepatitis B core antibody positive 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.

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 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.

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 (e.g., palpitations, lightheadedness) or new onset dyspnea.

Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. During visits in which both ECGs and blood draws are performed, ECGs should be performed first. Abnormalities noted at Screening should be included in the medical history.

7.1.3.2. Bone Marrow Aspirate/Biopsy

A bone marrow aspirate/biopsy, clot section, flow cytometry, cytogenetics, FISH, molecular studies and minimal residual disease (MRD) studies will be obtained at screening within 14 days before the first dose of ibrutinib, on Cycle 1 Day 8 (±1 days), Cycle 1 Day 49 (±3 days), Cycle 2

Day 42 (±3 days), Cycle 5, Day 42 (±3 days) or as clinically indicated to assess disease status per institutional guidelines.

Subjects with prolonged myelosuppression (≥ 49 days) and hypocellular bone marrow (i.e. cellularity 5% or less without evidence of disease) at the Cycle 2 day 1 assessments must undergo an additional bone marrow assessment on Cycle 1 Day 63 (±3 days) after initiation of study treatment.

7.1.4. Pharmacokinetics/Biomarkers

7.1.4.1. Pharmacokinetics

Pharmacokinetics samples will not be obtained on this study as previously described in Section 3.

7.1.4.2. Biomarkers

Identification of biomarkers that predict sensitivity or resistance to ibrutinib will be explored in this study. Exploratory investigations of predictive biomarkers will be tested in peripheral blood and bone marrow. Samples will be collected from all subjects. Peripheral blood and bone marrow aspirate will be collected at the time points specified in the Schedule of Assessment (Appendix 1).

Peripheral blood (PB) will be collected during screening, on Cycle 1, Day 8 (±1 day), Cycle 1, Day 36 (±3 days), Cycle 1, Day 49 (±3 days), days 28 and 42 of Cycles 2-5 (±3 days), and at treatment failure. Additional samples can be collected during unscheduled disease assessments at the investigator's discretion. Up to 50mL of PB will be collected in 3 x 10mL lavender top EDTA tubes (BD# 366643) and 2 x 8mL BD Vacutainer CPT with Na Citrate tubes (BD# 362761). PB EDTA tube samples (3 x 10mL) will be labeled with the patient ID number and shipped overnight on ice to the Molecular Pharmacology Shared Resource (MPSR) at UC Davis for processing below (Appendix 10). PB CPT tube samples (2 x 8mL) will be processed and shipped to Pharmacyclics as described in Appendix 11.

PB samples will be processed to isolate plasma and PB mononuclear cells (PBMC). Tubes will be inverted several times and placed on wet ice until ready to centrifuge. Tubes will be centrifuged at 800 x g for 10 minutes. Plasma will be transferred into a 15mL conical tube (labeled with the patient ID number) and centrifuged a second time at 800-1500 (preferred) x g for 10 minutes. Up to 10 x 500-1000µL aliquots of EDTA plasma will be transferred to cryovials labeled "Plasma" and with Study ID, patient ID, and date/time of draw. Samples will be stored at -80°C.

To isolate the PBMC, phosphate buffered saline (PBS) will be added to the cell pellet from the initial spin to bring the sample back up to the original volume. At this point, reagents and the samples will be brought to room temperature. Standard density centrifugation protocols will be used to isolate the PBMC. Briefly, 10mL of Ficoll (Amersham 17-1440-03) will be added to

each of two 50mL conical tubes. Each 10mL tube of PB plus PBS will be diluted with another 10mL of PBS (80mL total). Up to 40mL of PB diluted in PBS will be gently layered on top of the Ficoll in each of the two 50mL conical tubes. The sample is then centrifuged at 1500 rpm with no brake for 25 minutes. The interphase containing the mononuclear cells will be transferred from each tube to one new 50mL conical and diluted in 25mL of "Sample Buffer" consisting of PBS plus 2% fetal bovine serum (FBS). The sample is then centrifuged for 10 minutes at 1500 rpm. The pellet will be resuspended in 4mL of "Freezing Medium" consisting of 90% FBS plus 10% DMSO. 4 x 1mL aliquots of cells in Freezing Medium will be transferred to cryovials labeled PBMC and with Study ID, patient ID, and date/time of draw. Cryovials will be placed in a freezing chamber overnight at -80°C and transferred to liquid nitrogen storage the following day.

Bone marrow (BM) aspirates will be collected during screening, on Cycle 1, Day 8 (±1 days), Cycle 1, Day 49 (±3 days), Cycle 2, Day 42 (±3 days), Cycle 5, Day 42 (±3 days), and at treatment failure. Additional samples can be collected during unscheduled disease assessments at the investigator's discretion. Up to 15mL of BM aspirate will be collected in 3 x 6mL green top heparin tubes (BD# 367878). BM heparin tube samples will be labeled with the patient ID number and shipped overnight on ice to the MPSR for processing below (Appendix 10). In addition, 10 unstained slides cut at 5 microns each should be prepared from the BM core biopsy formalin-fixed paraffin embedded (FFPE) block. Slides will be labeled with the patient ID number and shipped overnight at ambient temperature to the MPSR (Appendix 10).

BM samples will be processed to isolate BM plasma and BM mononuclear cells (BMMC). Tubes will be inverted several times and placed on wet ice until ready to centrifuge. Tubes will be centrifuged at 800 x g for 10 minutes. Plasma will be transferred into a 15mL conical tube (labeled with the patient ID number) and centrifuged a second time at 800-1500 (preferred) x g for 10 minutes. Up to 10 x 500-1000µL aliquots of heparin BM plasma will be transferred to cryovials labeled "BM Plasma" and with Study ID, patient ID, and date/time of draw. Samples will be stored at -80°C.

To isolate the BM mononuclear cells (BMMC), standard density centrifugation protocols will be used. Samples and reagents will be brought to room temperature. 10mL of Ficoll will be added to a 50mL conical tube. BM aspirate will be diluted with an equal volume of PBS (approximately 30mL total). The BM aspirate cell pellet (after centrifugation to separate from BM plasma as above) diluted in PBS (approximately 30mL) will be gently layered on top of the Ficoll in the 50mL conical tube. The sample is then centrifuged at 1500 rpm with no brake for 25 minutes. The interphase containing the mononuclear cells will be transferred to a new 50mL conical and diluted in 25mL of Sample Buffer. The sample is then centrifuged for 10 minutes at 1500 rpm. The cells will be resuspended in 15mL PBS. 5mL (33% of the total sample) will be transferred to a 15mL conical and pelleted by centrifugation for 10 minutes at 1500 rpm. The pellet will then be resuspended in 3mL of Freezing Medium. 3 x 1mL aliquots of cells in Freezing Medium will be transferred to cryovials labeled BMMC and with Study ID, patient ID, and date/time of draw. Cryovials will be placed in a freezing chamber overnight at -80°C and transferred to liquid

nitrogen storage the following day. The remaining 10mL (67% of the total sample) of cells will be used to isolate CD19+ cells using a CD19+ selection kit (e.g. EasySep™ Human CD19 Positive Selection Kit, STEMCELL Technologies, catalog #18054). After washing, the CD19+ cell fraction and the CD19- cell fraction will both be divided into three equal aliquots. The three aliquots each from the CD19+ cell fraction and the CD19- cell fraction will be pelleted by centrifugation for 10 minutes at 1500rpm. The supernatant will be carefully removed (as much as possible) and the pellets frozen at -80°C. One of each aliquot of CD19+ and CD19- cells will be shipped to Pharmacyclics as described in Appendix 11.

BM core biopsy slides will be stored at ambient temperature at the MPSR.

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 including, but not limited to, flow cytometry, gene expression profiling, reverse phase protein assays, multiplex cytokine assays, 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. Specific planned analyses will be discussed in Section 10.7.

7.2. Efficacy Evaluations

A bone marrow aspirate/biopsy will be obtained at screening within 14 days before the first dose of ibrutinib. Follow up bone marrow examination for efficacy evaluation will be performed as described in the Schedule of Assessment (Appendix 1) until designation of TF or withdraw of consent. Peripheral blood and bone marrow aspirate smears will be examined morphologically for changes in blood counts using routine diagnostic procedures at the investigative site. Determination of response will be made by the Investigator according to the NCCN Guidelines for Acute Lymphoblastic Leukemia, Version 2.2015 (37). Response criteria for lymph node and other extramedullary disease are derived from the International Working Group revised response criteria for malignant lymphoma (38).

Disease Response Criteria:

<u>Bone Marrow and Blood</u>

Complete Remission (CR):

- No circulating blasts or extramedullary disease
- Bone marrow with normal trilineage hematopoiesis and <5% blasts
- Absolute neutrophil count (ANC) >1,000/microliter
- Platelet count >100,000/microliter
- No disease recurrence for 28 days

Complete Remission with Incomplete Blood Count Recovery (CRi): As for CR but platelet count <100,000/microliter or ANC <1,000/microliter

Complete Remission with Partial Hematologic Recovery (CRh): As for CR but platelet count >50,000/microliter and ANC >500/microliter

Overall Response Rate (ORR): Defined as the sum of the CR rate and CRi rate or the sum of the CR rate and CRh rate.

Refractory disease: Failure to achieve CR at end of induction

Progressive Disease (PD): Increase of at least 25% in the absolute number of circulating or bone marrow leukemic blasts or appearance of new extramedullary disease

Relapsed Disease: Re-appearance of blasts in the bone marrow (>5%) or blood or in any extramedullary site after achieving a CR or CRi

Flow MRD Negativity: Absence of detectable leukemic blasts above 0.01% (1x10-4) of bone marrow mononuclear cells by flow cytometry or molecular analysis.

CNS Disease

CNS Remission: Achievement of CNS-1 disease status in a patient with CNS-2 or CNS-3 disease status at diagnosis

CNS Relapse: New development of CNS-3 disease status or clinical signs of CNS involvement such as cranial nerve palsy, brain involvement, eye involvement, or hypothalamic syndrome. Whenever possible, clinical signs of CNS involvement without concomitant CSF involvement should be confirmed by biopsy. Otherwise, attribution of CNS symptoms to leukemia/lymphoma and requirement for treatment will be based on investigator judgment.

Mediastinal Disease

Complete Response: Complete resolution of mediastinal enlargement by CT or if FDG-avid/PET positive prior to therapy, mass of any size permitted if PET negative

Complete Response Unconfirmed (CRu): Residual mediastinal enlargement that has regressed by >75% in the sum of the product of the greatest perpendicular diameters (SPD)

Partial Response (PR): >50% decrease in the SPD of the mediastinal enlargement

Progressive Disease (PD): >25% increase in the SPD of the mediastinal enlargement

No response (NR): Failure to qualify for CR, CRu, PR, or PD

Relapse: Recurrence of mediastinal enlargement after achieving CR or Cru

Nodal Disease

Complete Response: Complete resolution of lymph node enlargement by CT or, if FDG-avid or PET positive prior to therapy, lymph node enlargement of any size permitted if PET negative

Partial Response (PR): ≥50% decrease in the SPD of up to 6 largest dominant masses with no increase in size of other nodes

Progressive Disease (PD) or Relapse: any new enlarged lymph node mass >1.5 cm in any axis, ≥50% increase in the SPD of more than one node, or ≥50% increase in the longest diameter of a previously identified node >1 cm in short axis OR lesions PET positive if FDG-avid or PET positive prior to therapy.

No response (NR): Failure to qualify for CR, PR, or PD

Other Extramedullary Disease (e.g. Spleen, Liver)

Complete Response: Complete resolution of disease by CT or, if FDG-avid or PET positive prior to therapy, lymph node enlargement of any size permitted if PET negative

Partial Response (PR): ≥50% decrease in the SPD of up to 6 largest dominant masses with no increase in size of other masses. If single mass then ≥50% decrease in greatest transverse diameter. No increase in size of liver or spleen.

Progressive Disease (PD) or Relapse: >50% increase from nadir in the SPD of any previous lesions

No response (NR): Failure to qualify for CR, PR, or PD

7.3. Sample Collection and Handling

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

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 Schedule of Assessments (Appendix 1) summarizes the frequency and timing of adverse event, safety measurements, biomarker, and procedures that are applicable to this study.

8.2. Screening Phase

Screening procedures will be performed up to 14 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
- 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)
- Complete physical exam including height and weight
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- Performance Status (KPS)
- 12-lead ECG. Subjects should be in a supine position and resting for at least 10 minutes before obtaining the ECG.
- Chest x-ray
- Imaging [CT (abdomen/chest, pelvis) and/or PET/CT] for patients with known lymphoblastic lymphoma or known extramedullary disease
- Bone marrow aspirate and biopsy, clot, flow cytometry, cytogenetics, FISH and molecular studies within 14 days before the first administration of study drugs
    - Bone marrow biomarker specimen
- Laboratory tests for:
    - Hematology including differential
    - Serum chemistries
    - Coagulation (PT/INR and PTT)
    - Serum or urine 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
    - HIV
    - Urinalysis
    - Peripheral blood biomarker specimen
- Review of eligibility criteria
- Confirm eligibility – complete enrollment checklist and submit to Sponsor for review/approval prior to enrollment

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.

8.3.1. Cycle 1, Day 1 Visit (±1 day)

- 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

- KPS status
- Confirm eligibility
- Laboratory tests for:
    - Hematology including differential (Subjects with platelet counts ≤30,000/μL at the beginning of any cycle will be required to have platelet assessment 2 times per week until the end of first treatment cycle. Any patient with platelets >30,000/μL who develops platelets ≤ 20,000/μL at any point during cycle 1 should begin having platelets evaluated two times per week each cycle until patient has a cycle where nadir is > 20,000/μL)
    - Serum chemistry
    - Pregnancy test (serum or urine)

- Dose administration – ibrutinib

- Provide drug diary and dosing instructions to subject
- Dispense study drug

8.3.2. Cycle 1, Day 8 Visit (±1 day)

- Review of current medications and any new medications since screening visit
- Review of current signs/symptoms including any new untoward events since screening
- Study drug compliance review
- Symptom directed exam
- Vital signs
- KPS status
- Bone marrow aspirate and biopsy, clot, flow cytometry, cytogenetics, FISH and molecular studies, and MRD analysis (note, formal response assessment will not occur at this time point and will occur with the cycle 1, day 49 time point as per Section 8.3.4).
    - Bone marrow biomarker specimen
- Laboratory tests for:
    - Hematology including differential (Subjects with platelet counts ≤30,000/μL at the beginning of any cycle will be required to have platelet assessment 2 times per week until the end of first treatment cycle. Any patient with platelets >30,000/μL who develops platelets ≤ 20,000/μL at any point during cycle 1 should begin having platelets evaluated two times per week each cycle until patient has a cycle where nadir is > 20,000/μL)
    - Serum chemistry
- PB biomarker specimen

- Dose administration – ibrutinib

- Dose administration – blinatumomab

8.3.3. Cycle 1, Day 15, 22, 29 and 36 Visits (±1 day)

- Review of current medications and any new medications since screening visit
- Review of current signs/symptoms including any new untoward events since screening
- Study drug compliance review

- Symptom directed exam
- Vital signs
- KPS status
- Laboratory tests for:
    - Hematology including differential (Subjects with platelet counts ≤30,000/μL at the beginning of any cycle will be required to have platelet assessment 2 times per week until the end of first treatment cycle. Any patient with platelets >30,000/μL who develops platelets ≤ 20,000/μL at any point during cycle 1 should begin having platelets evaluated two times per week each cycle until patient has a cycle where nadir is > 20,000/μL)
    - Serum chemistry
- PB biomarker specimen (day 36 visit ONLY)

- Dose administration – ibrutinib

- Dose administration – blinatumomab (dosing completed on day 35)

8.3.4. Cycle 1, Day 49 Visit (±3 days)

- Study drug compliance review
- Imaging [CT (abdomen/chest, pelvis) and/or PET/CT] for patients with known lymphoblastic lymphoma or known extramedullary disease
- Bone marrow aspirate and biopsy, clot, flow cytometry, cytogenetics, FISH, molecular studies, and MRD analysis
    - Bone marrow biomarker specimen
- Overall response assessment
- Laboratory tests for:
    - Hematology including differential (Subjects with platelet counts ≤30,000/μL at the beginning of any cycle will be required to have platelet assessment 2 times per week until the end of first treatment cycle. Any patient with platelets >30,000/μL who develops platelets ≤ 20,000/μL at any point during cycle 1 should begin having platelets evaluated two times per week each cycle until patient has a cycle where nadir is > 20,000/μL)
    - Serum chemistry
- PB biomarker specimen

- Dose administration – ibrutinib

8.3.5. Cycles 2-5, Day 1 Visit (±3 days)

- Review of current medications and any new medications since screening visit
- Review of current signs/symptoms including any new untoward events since screening
- Study drug compliance review
- Complete physical exam and weight
- Vital signs
- KPS status
- Laboratory tests for:

  - Hematology including differential (Subjects with platelet counts ≤30,000/μL at the beginning of any cycle will be required to have platelet assessment 2 times per week until the end of the treatment cycle. Any patient with platelets >30,000/μL who develops platelets ≤ 20,000/μL at any point during a cycle should begin having platelets evaluated two times per week each cycle until patient has a cycle where nadir is > 20,000/μL)
  - Serum chemistry

- Dose administration – ibrutinib

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

8.3.6. Cycles 2-5, Day 28 Visit (±3 day)

- Review of current medications and any new medications since screening visit
- Review of current signs/symptoms including any new untoward events since screening
- Study drug compliance review
- Symptom directed exam
- Vital signs
- KPS status
- Laboratory tests for:
  - Hematology including differential (Subjects with platelet counts ≤30,000/μL at the beginning of any cycle will be required to have platelet assessment 2 times per week until the end of the treatment cycle. Any patient with platelets >30,000/μL who develops platelets ≤ 20,000/μL at any point during a cycle should begin having platelets evaluated two times per week each cycle until patient has a cycle where nadir is > 20,000/μL)
  - Serum chemistry
- PB biomarker specimen (Cycles 2-5)

- Dose administration – ibrutinib

- Dose administration – blinatumomab (dosing completed on day 28)

8.3.7. Cycles 2-5, Day 42 Visit (±3 day)

- Study drug compliance review
- Imaging [CT (abdomen/chest, pelvis) and/or PET/CT] for patients with known lymphoblastic lymphoma or known extramedullary disease
  - Cycles 2 and 5 only
- Bone marrow aspirate and biopsy, clot, flow cytometry, cytogenetics, FISH, molecular studies, and MRD analysis
  - Bone marrow biomarker specimen
  - Cycles 2 and 5 only
- Overall response assessment
- Laboratory tests for:

  - Hematology including differential (Subjects with platelet counts ≤30,000/μL at the beginning of any cycle will be required to have platelet assessment 2 times per week until the end of the treatment cycle. Any patient with platelets >30,000/μL who develops platelets ≤ 20,000/μL at any point during a cycle should begin having platelets evaluated two times per week each cycle until patient has a cycle where nadir is > 20,000/μL)
  - Serum chemistry
- PB biomarker specimen (Cycles 2-5)

- Dose administration – ibrutinib

8.3.8. Maintenance Ibrutinib, Cycle 6+, Day 1 Visit (±3 day)

- Review of current medications and any new medications since screening visit
- Review of current signs/symptoms including any new untoward events since screening
- Study drug compliance review
- Complete physical exam and weight
- Vital signs
- KPS status
- Laboratory tests for:
  - Hematology including differential (Subjects with platelet counts ≤30,000/μL at the beginning of any cycle will be required to have platelet assessment 2 times per week until the end of the treatment cycle. Any patient with platelets >30,000/μL who develops platelets ≤ 20,000/μL at any point during a cycle should begin having platelets evaluated two times per week each cycle until patient has a cycle where nadir is > 20,000/μL)
  - Serum chemistry

- Dose administration – ibrutinib

- Provide drug diary and dosing instructions to subject
- Dispense study drugs

8.3.9. Treatment Failure Visit (±3 days)

- Review of concomitant medications
- Review of adverse events
- Study drug compliance review
- Complete physical exam
- Vital signs
- Performance Status (KPS)
- Bone marrow aspirate and biopsy, clot, flow cytometry, cytogenetics, FISH, molecular studies, and MRD analysis
  - Bone marrow biomarker specimen
- Overall response assessment
- Lab sample collection for
  - Hematology including differential
  - Serum chemistry

- PB biomarker specimen (Cycles 2-5)

8.3.10. End of Treatment Visit (30 days from last dose, ±7 days)

- Review of concomitant medications
- Review of adverse events
- Study drug compliance review
- Complete physical exam
- Vital signs
- Performance Status (KPS)
- 12-lead ECG. Subjects should be in a supine position and resting for at least 10 minutes before obtaining the ECG.
- Lab sample collection for
    - Hematology including differential
    - Serum chemistry

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) for up to 6 months and the following procedures should be performed.

- Complete physical exam including height and weight
- Vital Signs
- Performance Status (KPS)
- Survival status, including other malignancies
- Subsequent anticancer therapy
- Lab sample collection for
    - Hematology including differential
    - Serum chemistries
- Consider bone marrow aspirate and biopsy including bone marrow smear slides as clinically indicated

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, study termination by the Sponsor, or up to 6 months 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 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:

1. Unacceptable toxicity
2. Treatment failure or no evidence of clinical benefit per investigator assessment
3. An intercurrent illness or adverse event that prevents further ibrutinib administration.
4. Withdrawal of consent for treatment by subject
5. Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
6. Study termination by Pharmacyclics or study sponsor
7. 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.

9.3. Withdrawal from Study

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

1. Withdrawal of consent for follow-up observation by the subject
2. Lost to follow-up
3. Study termination by Pharmacyclics or study sponsor
4. 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:

1. Reason for withdrawal
2. Whether the subject withdraws full consent (i.e. withdraws consent to treatment and all further contact) or partial consent (i.e. withdraws consent to treatment but agrees to participate in follow-up visits)

10. STATISTICAL METHODS AND ANALYSIS

Statistical analysis will be done by the Investigator and Biostatistician. 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. Subject Information

Subject demographics (including age, sex, and race/ethnicity) and other baseline characteristics (including performance status, baseline blood and bone marrow features, 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 Endpoints

The primary objective is to evaluate the efficacy of ibrutinib and blinatumomab in patients with relapsed or refractory B-ALL. The primary endpoint is the rate of complete response (CR) within the first two cycles. Subjects who discontinue study therapy before the end of two cycles because of disease progression, death or adverse events related to treatment will be considered evaluable for response and included in the primary endpoint analysis. Subjects who discontinue study therapy for other reasons (e.g., withdrawal of informed consent) prior to having their first disease response assessment (e.g., Cycle 1 Day 49 visit, see Section 8.3.4) will not be considered evaluable for response, will not be included in the primary endpoint analysis, and will be replaced.

10.2.2. Secondary Endpoints

The secondary objective is to further examine the efficacy and safety of ibrutinib and blinatumomab in patients with relapsed or refractory B-ALL. Secondary endpoints include toxicity (graded according to the NCI CTCAE version 4.03 with DLTs defined as per Section 5.2.3), overall response rate (ORR, defined as CR plus CR with incomplete count recovery [CRi], or CR plus CR with partial hematologic recovery [CRh], as defined by disease-specific response criteria), relapse free survival (RFS, as measured by the time of CR/CRi until the date of progression or death from any cause), overall survival (OS, as measured from the time of first study drug administration until the date of progression or death from any cause), minimal residual disease (MRD) response (defined as B-ALL cells comprising greater than 0.01% of bone marrow mononuclear cells [BMMC] as measured by flow cytometry or molecular studies), and proportion of patients bridged to allo-HCT). Data for subjects who have not died will be censored at the date of last known contact for calculation of OS and RFS.

10.2.3. Exploratory Endpoints

The exploratory objectives are to examine the pharmacodynamic effects and of ibrutinib and blinatumomab in patients with relapsed or refractory B-ALL. Exploratory endpoints are BTK and ITK expression and occupancy analysis, and immune correlative analyses (plasma cytokines, flow cytometric analysis of T cell subsets and NK cells, and T cell functional assays).

10.3. Sample Size Determination

The primary endpoint for this study is CR rate. A 30% increase in CR rate compared to historical control with addition of ibrutinib would be clinically significant. A Simon's minimax two-stage design will be used (34). The null hypothesis that the true CR rate is 33% (historical control from (12)) will be tested against a one-sided alternative (12). In the first stage, 11 patients will be accrued (including the 6-9 patients from the safety lead-in). If there are 4 or fewer responses in these 11 patients, the study will be stopped. Otherwise, 7 additional patients will be accrued for a total of 18. The null hypothesis will be rejected if 10 or more responses are observed in 18 patients. This design yields a type I error rate of 0.05 and power of 0.8 when the true complete response rate is 63%.

Regarding the posited intervention effect, subgroup analysis from the registration study for Blinatumomab, which showed a 33% CR rate for the entire study population, showed a 73% CR rate if bone marrow blasts were less than 50% and a higher CR rate in subjects with higher CD3-positive cell percentages (12, 15). This study proposes a more modest increase to 63%, and the hypothesis of this study is that this effect is possible by the addition of ibrutinib to blinatumomab causing a direct anti-B-ALL effect and an indirect immunomodulatory effect.

Thus, the study will have a minimum sample size of 9 subjects and a maximum of 18 subjects. There will be 6-9 subjects in the safety lead-in cohort, and pending the interim analysis of response as per the Simon's two-stage design there will be a maximum of 18 subjects. The total sample size is 20, accounting for the possibility of subject drop out.

10.4. Efficacy Analysis

Methods for Evaluation of Measurable Disease

<u>Bone marrow</u>

Bone marrow aspiration of 2-3 ml should be prepared for standard morphologic evaluation by aspirate smears on glass slides. Additional aspirate (5-10 mL) should be obtained for flow cytometry, cytogenetics, molecular analyses and sendout MRD analysis. If bone marrow aspirate cannot be obtained (dry tap) or no spicules present in aspirate, 2 bone marrow core biopsies should be obtained for flow cytometry and cytogenetics. Institutional practice supersedes. Bone marrow core needle biopsy should be 1-2 cm in length for adequate evaluation.

Blood

Evaluation of peripheral blood should occur by morphologic evaluation of a peripheral blood smear. This should be performed at the time of each bone marrow biopsy and when clinically indicated.

Extramedullary Disease

Lymph node enlargement, tumors:

A PA/lateral chest X-ray will be performed at Screening for all study patients. For patients with a mediastinal mass on CXR or lymphadenopathy on physical exam, FDG-PET/CT scan will be performed with diagnostic CT scans of the chest, abdomen, and pelvis with IV contrast except when contraindicated or felt unsafe by the investigator. If unable to obtain PET/CT, diagnostic CT scans of the chest, abdomen, and pelvis with IV contrast should be obtained except when contraindicated.

For patients with pathologic lymph node enlargement or tumors, all measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

CNS disease:

CSF samples from lumbar punctures should be sent for cell count, total protein, glucose, and standard cytology with every lumbar puncture performed while patient remains on study.

Effusions:

When safe to do so, pleural effusions and ascites should be sampled and analyzed by standard cytology for evidence of disease. Cytologic evaluation of any effusion that appears or worsens during treatment when the measurable tumor has otherwise met criteria for complete response or stable disease is mandatory to differentiate between complete response and progressive disease.

Response Criteria

Response criteria for bone marrow, blood, CNS disease, mediastinal disease are from the NCCN Guidelines for Acute Lymphoblastic Leukemia, Version 2.2015 (37). Response criteria for lymph node and other extramedullary disease are derived from the International Working Group revised response criteria for malignant lymphoma (38). Please refer to Section 7.2 for details.

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. The safety analyses will be based on the monitoring of adverse events, survival status, 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, vital signs measurements, and reason for discontinuation of study drug (if applicable). Tables will be created to summarize the toxicities and adverse effects by dose, course, organ and severity. Descriptive statistics will be used, including mean, standard deviation, median, and minimum and maximum values for continuous variables and frequencies and percentages for categorical variables. No formal statistical testing is planned.

The first part of the study will be a safety-lead in cohort comprising the first 6-9 patients enrolled and treated. The rules of this cohort are described in Section 5.2.2 and 5.2.3. The intended study dose of ibrutinib 560mg in combination with blinatumomab will be tested in the first 6 patients. If 0-1 dose limiting toxicities (DLTs) are observed then the study will continue to accrue as per the Simon's two-stage design (Section 10.3). If 2 DLTs are observed in the first 6 patients, then 3 additional subjects will be assessed for DLTs. If 3 or more of the 9 subjects experience DLTs, enrollment will be halted at the 560mg dose level and an ibrutinib dose of 420mg will be considered. For the safety lead-in, if patients do not experience a DLT during cycle 1 but miss more than 25% of the total planned treatment doses for the cycle, they will be replaced.

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.

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, and 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, Version 4.03) 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. 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. All laboratory values will be converted to standard international units and will be graded using the NCI CTCAE Version 4.03. Standard methods for summarizing laboratory variables will be used, including the use of summary statistics.

10.6. Analysis of Secondary and Exploratory Endpoints

Because of the limited sample size inherent to this type of study, the analysis of secondary and exploratory endpoints is primarily exploratory. These studies are expected to be hypothesis supporting or generating for studies of larger patient cohorts, as a result of identifying trends in the data. This study cohort will allow us to better assess the toxicity. While the precision of the estimates of toxicity and response is limited with the numbers proposed, we will be able to establish general overall patterns for efficacy and correlative changes, particularly if the effect is dramatic. Tables will be created to summarize the toxicities and adverse effects by dose, course, organ and severity as well as the study demographics. Descriptive statistics will be used, including mean, standard deviation, median, and minimum and maximum values for continuous variables and frequencies and percentages for categorical variables. Survival analyses will be performed using the Kaplan-Meier method. These analyses will be applied to the primary, secondary, and exploratory/correlative endpoints described above. Baseline levels for various endpoints can be compared to changes after treatment which will allow us to examine whether observed patterns are consistent with our hypotheses, and if the agent is not found to have sufficient activity, then these patterns may help explain the lack of activity. If sufficient activity is found, then subjects who experience an objective response will be compared to those who did not in terms of the secondary and correlative endpoints that could help guide future research with this regimen. Formal testing of these comparisons is not planned however.

10.7. Biomarker Analyses

Samples will be obtained, processed, shipped, and stored as per Section 7.1.4.2 and Appendix 10 and Appendix 11 at times detailed in the Schedule of Assessments (Appendix 1). Planned biomarker analysis includes: (1) BTK expression, phosphorylation, and occupancy by ibrutinib in B-ALL cells; (2) ITK expression, phosphorylation and occupancy by ibrutinib in peripheral blood T cells; (3) changes in peripheral T cell subsets as determined by multicolor flow cytometry; (4) immune cell functional assays; and (5) multiplex plasma cytokine assays. Changes in biomarkers over time will be summarized and association between baseline levels and changes from baseline in select markers and response to treatment will be explored as described above in Section 10.6. Biomarker analysis will be performed at the MPSR (Director: Philip Mack, Ph.D.) or at Pharmacyclics. From each biomarker collection time point up to 4 aliquots of PBMC, up to 5 aliquots of BMMC, up to 10 aliquots of plasma, and 10 unstained BM core FFPE block slides will be stored for potential future unplanned correlative studies including, but not limited to, reverse phase protein arrays, T cell clonality assays, mutational analysis, immunohistochemistry, disease stem cell studies, and cytokine analysis.

Detailed descriptions of the biomarker assays are as follows:

BTK expression, phosphorylation, and occupancy by ibrutinib in bone marrow CD19+ cells (Performed by Pharmacyclics): we will assess on-target effects of ibrutinib in subjects with B-ALL. B-ALL will be isolated from fresh BMMC using a CD19+ selection kit as described in Section 7.1.4.2. One aliquot each from the CD19+ and CD19- cell fractions will be shipped to Pharmacycics as described in Appendix 11 for BTK expression, phosphorylation and occupancy studies (39).

ITK expression, phosphorylation and occupancy by ibrutinib in peripheral blood T cells (Performed by Pharmacyclics): we will assess off-target effects of ibrutinib in subjects with B-ALL. PBMC will be isolated from BD Vacutainer CPT with Na Citrate tubes and shipped to Pharmcyclics as described in Section 7.1.4.2 and Appendix 11 for ITK expression, phosphorylation and occupancy assays (31). At Pharmacyclics, CD3+ cells will be isolated from thawed PBMC using a CD3+ selection kit (e.g., EasySep™ Human CD3 Positive Selection Kit, STEMCELL Technologies, catalog #18051) prior to performing ITK assays.

Changes in peripheral T cell subsets as determined by multicolor flow cytometry (Performed by University of California Davis): we will assess whether there are changes in peripheral T cell subsets in patients with B-ALL treated with ibrutinib minus/plus blinatumomab. Fresh or thawed PBMC will be immunophenotyped for T cell subsets, including effector, activated, memory, exhausted and regulatory, and NK/NKT cells. Levels of various T and NK cell subsets will be reported as percentages of total PBMC and as percentages of total T cells in the case of T cell subtypes. Absolute numbers of each subtype will be determined by calculating the percentage as determined by flow cytometry by the total WBC on the day of sampling. Absolute lymphocyte counts will be calculated for each biomarker time point from the concurrent CBC with manual differential.

Specific immunophenotypes include:

Cell subset		**Phenotype marker**
T cell	$CD4^+$ helper T cell	$CD3^+CD4^+$
	$CD8^+$ cytotoxic T cell	$CD3^+CD8^+$
	Regulatory T cells	$CD3^+CD4^+CD25^+Foxp3^+$
	Naïve T cell	$CD4^+/CD8^+CD45RA^+CD11a^+$
	Memory T cell	$CD4^+/CD8^+CD45RO^+CD11a^+$
	NK T cell	$CD3^+CD56^+CD16^+$
	iNKT cell	$CD3^+CD56^+CD16^+6B11^+CD1d^+$

NK cell		$CD3^- CD56^+ CD16^+$
B cell	B2 cell	$CD19^+ IgD^+ CD11b^- CD5^-$
	B1a cell	$CD19^+ IgM^+ CD11b^+ CD5^+$
	B1b cell	$CD19^+ IgM^+ CD11b^+ CD5^-$

Immune Cell Functional Assays:

Assay of PBMC's for T cell and monocyte activation: PBMC's will be purified from blood as described in Section 7.1.4.2 and will be cultured in quadruplicate 96-well U-bottom plates for each condition: culture medium alone or medium supplemented with CD3/CD28 mAb (0.5 µg/ml), or PHA (5 µg/ml) for T cell activation and LPS (1ug/ml) for monocyte activation. Cells will be incubated for 3-5 days at 37°C, 5% CO2. The culture supernatants will be collected and stored at -70°C. The supernatants will be assayed for several cytokines/chemokines (e.g. IL-2, IFN-γ, IL-17, IL-10, IL-4, TNF-α, TGF-β) using the Multiplex Bead-based Luminex® Technology, Cytokine Human 10-Plex Panel (or if batched with other samples, the Cytokine Human 25-Plex Panel) (Invitrogen, Carlsbad, CA), see below.

NK functional assay: Human NK cells will be identified as described NK (CD3-CD56+CD16+), NKT (CD3+CD56+CD16+) and iNKT cells will be sorted from blood. The sorted NK/NKT cells will be stimulated with poly IC for 12 and 24 h. iNKT cells will be stimulated with iNKT cell-specific ligand, α-GalCer. Supernatants will be collected to analyze the levels of IFN-gamma, IL-6 and IL-8 using the BD cytometric bead array kit per the manufacturer's recommendations. IFN-gamma and IL-4 will be measured by CBA kit or intracellular staining. Sera cytokine will be measured by CBA kit.

NK Cell Killing Activity: NK cells bind to, and kill K562 cells (a human myelogenous cell line, ATCC) thus forming the basis of this functional killing assay; this flow cytometric assay can detect binding and killing.

Multiplex Plasma Cytokine Assays: Multiplex Bead-based Luminex® assay for immunologic analytes includes 37 different cytokines and growth factors (including IL-1, 2, 4, 5, 6, 7, 10,12, 17, TNF, INF-γ, TGF-beta, GM-CSF, PDGF, and VEGF) (Invitrogen). This test will allow for the ultrasensitive determination of cytokines in the plasma of patients before and during treatment with ibrutinib minus/plus blinatumomab. The microbead multiplex detection system developed by Invitrogen) enables detection of numerous cytokines simultaneously in a single reaction container. In this technology, molecular reactions take place on the surface of microscopic plastic beads (2 um). For each reaction, capture molecules (i.e., mono-specific antibodies) are covalently attached to the surface of internally color-coded microbeads. The assigned color-code identifies the reaction in a specific microbead population throughout the test. Multiplex capability involves mixing several populations of microbeads, each with a specific capture molecule, into one reaction vessel at the start of the test. The magnitude of the biomolecular reaction is measured using a reporter molecule which signals the extent of the reaction by attaching to the test molecules captured on the microbeads. To perform a test, the color-coded microbeads, reporter molecules, and sample (e.g., tumor cell lysate) are mixed and then injected into the Luminex flow cytometer where lasers illuminate the colors inside and on

the surface of each microbead. This method is rapid, sensitive, and quantitative, and lends itself to high-throughput in an economical fashion.

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 are mandated by regulatory agencies worldwide.

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. (http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073087.pdf)

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. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should 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.
- Record all AEs for any patient in Cycle 1. For Cycle 2 and beyond, record only highest grade of an individual toxicity.
- 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 (e.g., 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 International Conference on Harmonisation (ICH) (40) and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death (i.e., 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 IND Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.

- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.

- Results in persistent or significant disability/incapacity (i.e., 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 lifethreatening 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.

11.1.3. Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events v4.03 (CTCAE v4.03) will be used for grading the severity (intensity) of nonhematologic AEs. The CTCAE v4.03 will be used for the grading of hematologic AEs when applicable (See Section 5.2.3). 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 (i.e., 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 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 exposure to the study drug, e.g., name confusion)

Occurrence of any special reporting situations should be recorded in the eCRF. If any special reporting situation meets the criteria of an AE, it should be recorded on the AEs eCRF. If the AE is considered serious, it should be recorded on the AEs eCRF as serious and should be reported on the Serious Adverse Event Report Form. The Serious Adverse Event Report Form should be sent via email or fax to Pharmacyclics Drug Safety Pharmacovigilance & Epidemiology (DSP&E) within 15 days 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 time points 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 AEs 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 (i.e., 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 captured from the time of first dose of study treatment until 30 days following the last dose of study drugs. 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 (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

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.

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

11.4.3. 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 after the last dose of study drugs. 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 female subject or female partner of a male subject from the time of consent to 90 days after the last dose of study drugs must be reported. Any

occurrence of pregnancy must be reported to Pharmacyclics Drug Safety Pharmacovigilance & Epidemiology (DSP&E) per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing will need to be reported to Pharmacyclics per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

11.4.4. 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 post-progression follow-up for overall survival. If observed, enter data in the corresponding eCRF.

11.4.5. 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 Pharmacovigilance & Epidemiology (DSP&E) within 15 days of awareness.

11.4.5.1. Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events 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 below.

11.4.6. Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email (AEintakePM@pcyc.com) or fax ((408) 215-3372) to Pharmacyclics Drug Safety Pharmacovigilance & Epidemiology (DSP&E), or designee, within 15 days of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

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)

Reporting to Regulatory Agencies:

Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

It is the responsibility of the IND Sponsor to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines and the study sponsor's guidelines.

Reporting to the Institutional Review Board

Both serious and non-serious adverse events will be reported in accordance with UCD IRB Administration and UCD Cancer Center OCR policies. The UC Davis IRB can be reached at (916) 703-9151.

Participating site(s) will report adverse events per institution's IRB guidelines.

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 with the ethical principles laid down in the Declaration of Helsinki.

12.2. Study Registration

Registration will be done centrally at UC Davis. Once signed, informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study according to Office of Clinical Research (OCR) policy. To register a patient, the data manager or designee must complete the Eligibility Checklist and the Patient Registration Form. After verifying the eligibility, the OCR coordinator will register the patient onto the study and assign a patient accession number. Administration of study drug may not be initiated until the patient is registered (See Appendix 8).

12.3. Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). In accordance with UCD OCR policy an original signed and dated participant Informed Consent document will reside in a secured location within the UCD OCR. Participating sites will store original signed and dated informed consent per its policies. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information Management for inclusion in the participant's UCD Health System Medical Record or per participating site's policies.

12.4. Study Files and Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

12.5. Protocol Deviations

All protocol deviations will be reported in accordance with UCD IRB Administration and UCD Cancer Center OCR policies or the participating site's IRB policies.

12.6. Data Submission

All data will be collected using the UCD Database System (eVELOS) forms. All data forms will be completed, submitted and processed in accordance with UCD OCR policies. See Appendix 9 for Data Collection Schedule.

12.7. Investigational Study Drug Accountability

Ibrutinib will be supplied by Pharmacyclics. Ibrutinib 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 to other

Investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Pharmacyclics.

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
2. Subject identification number
3. Lot number(s) of ibrutinib dispensed for that subject
4. Date and quantity of drug dispensed
5. Any unused drug returned by the subject

12.8. Quality Assurance and Control

Quality assurance audits of select patients and source documents may be conducted by the UC Davis Cancer Center Quality Assurance Committee as outlined in the UC Davis Cancer Center Data and Safety Monitoring plan.

Quality control will be maintained by the OCR Quality Assurance team according to OCR policy.

12.9. Data and Safety Monitoring

In addition to the requirements for adverse event reporting as outlined in Section 11, this protocol is also subject to the UC Davis Cancer Center's (UCDCC) Data and Safety Monitoring Plan. The UCDCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCC to fulfill its mission in conducting high quality clinical cancer research.

As per University of California Davis Cancer Center (UCDCC) SOP AM 506: Protocol Specific Meetings, the principal investigator (PI) and clinical research coordinator (CRC) meet at least monthly for ongoing study information, to discuss patient data and adverse events and to determine if dose escalation is warranted, when applicable.

According to the UCDCC Data and Safety Monitoring Plan (DSMP), any new serious adverse events related to the drugs being used on this trial are reviewed monthly by the UCDCC Data

and Safety Monitoring Committee (DSMC) and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCC Scientific Review Committee (SRC) determines if a UCDCC Data and Safety Monitoring Board (DSMB) is required. If required, the DSMC will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, adverse event information and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

12.10. Patient Confidentiality

In order to maintain patient privacy, all study reports and communications will identify the patient by initials and the assigned patient number. Data capture records and drug accountability records will be stored in secure cabinets in the UCD Office of Clinical Research or at the participating institutions. Medical records of patients will be maintained in strict confidence according to legal requirements. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.11. Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Per the IST Agreement, any amendments to the Protocol or Informed Consent Form must be sent to Pharmacyclics for review and approval prior to submission to the IRB. Written verification of IRB approval will be obtained before any amendment is implemented.

12.12. Protocol Amendments

Per the IST Agreement, any amendments to the Protocol or Informed Consent Form must be sent to Pharmacyclics for review and approval prior to submission to the IRB. Written verification of IRB approval will be obtained before any amendment is implemented.

12.13. Publication of Study Results

Per the IST Agreement, the Investigator is required to submit to Pharmacyclics a copy of a planned publication (abstract, poster, oral presentation or manuscript) prior to the submission thereof for publication or disclosure. Pharmacyclics may provide scientific comments and suggestions understanding that the Investigator has sole editorial responsibility, and retains the authority to make the final determination on whether or not to incorporate Pharmacyclics comments or requests for additional information.

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14. APPENDICES

Appendix 1. Schedule of Assessments

Study Cycle		C1							C2-5			C6+	TF	EOT[a]	RFU[b]	LTFU[q]
Study Day		D1	D8	D15	D22	D29	D36	D49	D1	D28	D42	D1	Any Time	30 days from last dose		
Visit Windows		±1 day						±3 days	±3 days					±7 days	±14 days	
	Screening Phase Day -14 to 0															
	Study Drug Administration															
Ibrutinib[r]		x	x	x	x	x	x	x	x	x	x	x				
Blinatumomab[r]			x	x	x	x			x	x						
	Procedures															
Informed Consent	x															
Medical History and demographics	x															
Review concomitant medications	x	x	x	x	x	x	x		x	x		x	x	x		
Review Adverse Events		x	x	x	x	x	x		x	x		x	x	x		
Study Drug Compliance Review			x	x	x	x	x	x	x	x	x	x	x	x		
Complete Physical Exam, with weight[d]	x	x							x			x	x	x	x	
Symptom directed exam			x	x	x	x	x			x						
Vital Signs	x	x	x	x	x	x	x		x	x		x	x	x	x	
Performance Status	x	x	x	x	x	x	x		x	x		x	x	x	x	

Study Cycle		C1							C2-5			C6+	TF	EOT[a]	RFU[b]	LTFU[q]
Study Day		D1	D8	D15	D22	D29	D36	D49	D1	D28	D42	D1	Any Time	30 days from last dose		
Visit Windows		±1 day						±3 days	±3 days					±7 days	±14 days	
	Screening Phase Day -14 to 0															
ECG[e]	x													x		
Chest x-ray[f]	x															
Bone Marrow Biopsy and Aspirate and flow cytometry[g]	x		x					x			x[g]		x[g]			
Overall disease/response assessment[h]	x							x			x[h]		x			
Confirm eligibility	x	x														
Survival Status[i]															x	x
Subsequent Cancer Therapy															x	x
Hematology[j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum Chemistries[k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Coagulation Studies	x															
Hepatitis Serology[l]	x															
HIV[m]	x															
Urinalysis[n]	x															
Pregnancy Tests	x	x														
Biomarker – peripheral blood[o]	x		x				x	x		x	x		x			

Study Cycle		C1							C2-5			C6+	TF	EOT[a]	RFU[b]	LTFU[q]
Study Day		D1	D8	D15	D22	D29	D36	D49	D1	D28	D42	D1	Any Time	30 days from last dose		
Visit Windows		±1 day						±3 days	±3 days					±7 days	±14 days	
	Screening Phase Day -14 to 0															
Biomarker – bone marrow[p]	x		x					x			x		x			

Abbreviations: C = cycle, D = day, TF = treatment failure, EOT = end-of-treatment, RFU = response follow up, LTFU = long-term follow up, ECG = electrocardiogram

a. An EOT visit will occur 30 ± 7 days 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) up to 6 months until TF or use of alternative cancer treatment.
c. Footnote c removed.
d. 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.
e. Subjects should be in a supine position and resting for at least 10 minutes before obtaining the ECG. During the treatment period, ECG's may be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea. A single ECG tracing will be performed at EOT
f. Chest x-ray at screening for all patients.
g. Bone marrow biopsy and aspirate, clot section, flow cytometry, cytogenetics, FISH, molecular and MRD analysis should be completed during screening period within 14 days of initial drug dose (pre-C1D1), C1D8, C1D49, C2D42, C5D42, at disease progression/treatment failure, or at other times at Investigator discretion.
h. Complete Response assessment should be performed with all bone morrow biopsies except the Cycle 1 Day 8 biopsy. Patients with known lymphoblastic lymphoma or known extramedullary disease will have high resolution CT (chest, abdomen, pelvis) and/or PET/CT at baseline and at time of disease assessment on Cycle 1 Day 49, Cycle 2 Day 42, and Cycle 5 Day 42.
i. Includes assessment for development of other malignancy.
j. Hematology includes complete blood count with differential and platelet counts. Subjects with platelet counts ≤30,000/µL at the beginning of any cycle will be required to have platelet assessment 2 times per week until the end of first treatment cycle. Any patient with platelets >30,000/µL who develops platelets ≤ 20,000/µL at any point during cycle 1 should begin having platelets evaluated two times per week each cycle until patient has a cycle where nadir is > 20,000/µL.
k. 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.
l. 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.
m. Any positive HIV test should be confirmed by western blot.
n. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
o. Peripheral blood biomarker samples should be drawn pre-C1D1, C1D8, C1D35, C1D49 and days 28 and 42 of Cycles 2-5 (-/+1 day in cycle 1 and -/+3 days in cycles 2-5). Up to 50mL peripheral blood will be collected for evaluation. Biomarker samples are optional for unscheduled diseases assessments but should be obtained at treatment failure.
p. From the bone marrow biopsy, up to an additional 10 unstained slides and up to 15mL aspirate samples will be collected for evaluation. Biomarker samples are optional for unscheduled bone marrow biopsies but should be obtained at treatment failure.

q. Long term follow up will be 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, study termination by Pharmacyclics or the study sponsor, or up to 6 months, whichever occurs first.

r. Ibrutinib is given days 1-49 of cycle 1 and days 1-42 of cycles 2-5. Blinatumomab is given days 8-35 of cycle 1 and days 1-28 of cycles 2-5.

Appendix 2. KPS and ECOG Status Scores*

Karnofsky Status	Karnofsky Grade**	ECOG Grade	ECOG Status**
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80		
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40		
Severely disabled. Hospitalization indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20		
Moribund	10		
Dead	0	5	Dead

* KPS will be used in this study. ECOG status is listed for reference.

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Appendix 3. Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 6.2.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib.

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	

Inhibitors of CYP3A	**Inducers of CYP3A**
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	

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

Appendix 4. Child-Pugh Score

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, Pietroni MC, Williams R . "Transection of the oesophagus for bleeding oesophageal varices". *The British journal of surgery*, 1973;60: 646-9.

Appendix 5. Cockcroft-Gault estimation of CrCl

Cockcroft-Gault estimation of creatinine clearance (CrCl):
(Cockcroft, 1976; Luke 1990)

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \quad \textbf{(Males)}$$

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85 \quad \textbf{(Females)}$$

Appendix 6. NCI CTC Version 4.03

Toxicity will be scored using NCI CTC version 4.03 for toxicity and adverse event reporting. A copy of the NCI CTC version 4.03 can be downloaded from the CTEP homepage: (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTC version.

Appendix 7. Pill Diary

PROTOCOL TITLE: **A Phase 2 Study of Ibrutinib and Blinatumomab in Relapsed and Refractory B-Cell Acute Lymphoblastic Leukemia**

PROTOCOL NUMBER: UCDCC#266

PATIENT NAME: _____

MEDICAL RECORD NUMBER: _____

INVESTIGATIONAL AGENT: Oral ibrutinib

CYCLE #: _____ **START DATE:** _____ **DOSE:** _____

Instructions: Ibrutinib is an oral agent that should be taken once daily every day (49 days for cycle 1, 42 days for cycles 2-5 and 28 days for cycles 6+). It should be taken around the same time each day. Please indicate in the corresponding box using a check mark the days that you took ibrutinib. If you miss a dose, do not double up the next dose. Just leave the corresponding box for the missed dose blank.

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Initials														
Day	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Initials														
Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Initials														
Day	43	44	45	46	47	48	49							
Initials														

Note: Days 1-49 on cycle 1 only, Days 1-42 on cycles 2-5 and Days 1-28 only on cycles 6+

PATIENT SIGNATURE: _____ **DATE:** _____

Appendix 8. Registration Guidelines

A. Before registration, the site study coordinator should check to make sure that the corresponding Investigational Drug Service or equivalent has study drug in stock.

B. Registrations for this Phase I protocol must be made through the Office of Clinical Research (OCR) of the University of California, Davis Comprehensive Cancer Center between the hours of 9am and 3pm (Pacific Time), Monday through Friday (except holidays). Documentation of current IRB approval of this protocol by non-UC Davis institutions must be on file prior to registration of patients at these institutions.

C. Pre-study laboratory tests, scans, and x-rays, must be completed prior to registration, within the time frame specified in the protocol. The eligibility checklist must be completed. Patients must sign an informed consent prior to registration.

D. Patients may be registered up to 72 hours prior to treatment initiation. All pages of the signed consent, completed checklist and reports from all pre-study laboratory tests, scans and x-rays must be faxed to UC Davis OCR ([redacted] or emailed to UCD in order to register the patient. These documents are to be redacted and "patient initials" or "a participating site subject identifier" will be written on the documents until the Study Subject ID is issued. The UC Davis Study Coordinator will review these documents and fax/email a registration confirmation within 24 hours.

   Reminder: Confirm eligibility for ancillary studies and willingness to participate at the same time as eligibility for the treatment study.

E. If the patient is to be registered the same day as the proposed treatment start date, the UC Davis Study Coordinator must be notified by fax 24 hours prior to proposed treatment start date that the site has a patient to register.

F. The Study Coordinator will verify that the patient is eligible, that pre-study tests have been completed, and that the forms are complete. The Study Coordinator will then register the patient and assign a patient accession number. The Study Coordinator will fax or email a registration confirmation including the patient accession number within 24 hours.

G. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact the coordinating site PI or Study Coordinator.

NOTE: Administration of study medication may not be initiated until the registration confirmation has been received.

Appendix 9. Data Submission Schedule

All data will be collected using UC Davis data collection forms. The collection forms are pdf editable forms that can be faxed/emailed to UCD. Copies of the completed forms will be submitted to UC Davis data coordinating center for data entry and storage in a secure location. The original data collection forms will reside in secure location.

- SUBMIT WITHIN 24 HOURS OF REGISTRATION:

  Patient Registration Form
- SUBMIT WITHIN 14 DAYS OF REGISTRATION:

  Pre-Study Evaluation Form
- SUBMIT WITHIN 7 DAYS OF SCREENING FAILURE:

  Patient Screen Failure Form
- SUBMIT WITH 14 DAYS OF CYCLE COMPLETION:

  Adverse Event/Drug Relationship Form
- SUBMIT WITHIN 14 DAYS OF END OF EACH TREATMENT CYCLE:

  Treatment Cycle Form – Oral

  Treatment Cycle Form - Infusion
- SUBMIT WITHIN 14 DAYS OF EACH RESPONSE ASSESSMENT:

  Tumor Measurement Log
- SUBMIT WITHIN 14 DAYS OF OFF TREATMENT:

  Off Treatment/In Follow-up/Off Study/Expiration Form
- SUBMIT WITHIN 14 DAYS OF KNOWLEDGE OF DEATH IF PATIENT IS STILL ON STUDY OR 30–DAYS IF OFF STUDY:

  Off Treatment/In Follow-up/Off Study/Expiration Form
- SUBMIT WITHIN 2 DAYS OF KNOWLEDGE OF PROTOCOL DEVIATION:

  Notice of Protocol Deviation
- SUBMIT WITHIN 14 DAYS OF EACH REQUIRED FOLLOW-UP ENCOUNTER:

  Follow-Up Form
- ALL SERIOUS ADVERSE EVENTS MUST BE REPORTED AS OUTLINED IN THE PROTOCOL
- ADDITIONAL STUDY- SPECIFIC CASE REPORT FORMS ARE CURRENTLY UNDER DEVELOPMENT

Appendix 10. UC Davis Sample Submission Form

Patient Information:

Patient Study ID# _____ **Pt Initials (FML):** _____

Timepoint:

☐ Screening ☐ Cycle # _____ (collect on day 1 of cycle 2, and day 28 of 4 and 6)

☐ Progression ☐ Unscheduled Assessment Cycle #_____

Draw Date: **Time of Draw:**

Shipper Contact Information:

Packaged by: _____ Phone #: _____ Email Address: _____

Specimen Collection and Processing Instructions:

Draw: **3 x 10 ml (30mL) Purple EDTA Tube (Peripheral Blood)** (BD# 366643)
3 x 6 mL (up to 10mL) Green top Heparin Tube (BM aspirate) (BD# 367878)

EDTA and Heparin tubes: Invert tubes several times and place at 4°C. Please ensure that tubes are completely labeled with patient Study ID, initials (FML), and the date/time of draw. Remove any other identifying information (name, medical record number, date of birth, etc.).

Slide Submission: please have 10 unstained slides cut at 5 microns each.

Packaging shipment: Refrigerated specimens should be shipped immediately to UC Davis. Please ship with ice packs and with tubes in sealed specimen bags filled with ice. If the sample is collected on a Friday or weekend day, please place at 4°C and ship on Monday. FFPE BM slides may be sent at ambient temperatures with a room-temperature gel pack to protect specimen from temperature fluctuations. In summer months when outdoor temperatures can exceed 90°F, please pack specimens with a refrigerated gel pack. FFPE samples can be batched and shipped to UCD periodically on Mon-Wed.

When shipping, please send email notification including FedEx tracking number to:

[redacted]

Packaged Specimens should be shipped using **FedEx Priority**

[redacted]

Molecular Pharmacology Shared Resource Use Only

Lab Specimen #_____ **Date Received:** ☐☐/☐☐/☐☐

Condition of Specimen:

☐ **Usable as received** **Received/Logged By:** _____

☐ **Usable, not optimal:** _____

Appendix 11. Pharmacyclics Sample Submission Form

PD Sample Collection Procedures

Collection of PBMC and Plasma from patient blood samples for occupancy assays

Collect the PD blood samples for occupancy assays according to the time points described in the protocol.

USE **2 x 8-m**L BD Vacutainer CPT Cell Preparation Tubes with Sodium Citrated FOR EACH PD COLLECTION PER PATIENT

NOTE: All centrifugation processes are to be done at room temperature (RT)

1. Allow tube to fill COMPLETELY, as far as the vacuum will allow.

2. Mix the tube immediately upon completion to avoid clotting by inverting gently 5 times.

DO NOT SHAKE.

3. Centrifuge blood collection tubes at 2,700 rpm for 20 min at RT in the swing rotor with no brake

PLASMA SAMPLES:

4. Transfer 1.5 ml plasma with pipette to a 2-mL cryotube from each CPT tube (Total of 2 cryotubes)

5. Enter the Subject ID number on the sample labels.

6. Store at -70˚C or below within approximately 60 minutes of blood collection

7. Ship samples **FROZEN** to **Pharmacyclics**

PBMC BAND:

8. Transfer the "PBMC band" with pipette to a new 15 mL Falcon tube

9. Re-suspend with 10 -13 mL of D-PBS to the 15 mL Falcon tubes (Total of 2 Falcon tubes)

10. Centrifuge tubes at 1,500 rpm for 5 min at RT with brake

11. Aspirate supernatant completely without disturbing cell pellet

12. Gently tap the bottom of tubes and then add 1 mL of RBC lysis buffer to each tube

13. Gently pipette to obtain uniform suspension, and then combine 2 PBMC suspensions to one Falcon tube

14. Incubate at RT for 5 min

15. Add 12 mL of D-PBS to the tube, invert once

16. Centrifuge the tube at 1,500 rpm for 5 min at RT with brake

17. Aspirate supernatant

18. Centrifuge the tube for 1 min at 1,500 rpm to pull down all residual fluid to the bottom of tubes

19. Aspirate supernatant as much as possible (**VERY IMPORTANT**)

20. Enter the Subject ID number on the sample labels.

21. Store tubes at -70°C or below, within approximately 60 minutes of blood collection.

22. Ship samples **FROZEN** to **Pharmacyclics**

All time points

Sample	COLLECT	PREPARE	CONTAINER	SHIP TEMP
Plasma (PD)	2 x 8 mL BD Vacutainer CPT with Na Citrate 	Centrifuge and transfer	2 x 1.8 mL Cryotubes 	Frozen
PBMC BAND (Occupancy)		Centrifuge, transfer, RBC lysis and wash	2 x 15 mL Falcon tubes 	Frozen

Shipping Instructions for samples of plasma and PBMC for occupancy assays

Samples should be shipped on dry ice **Monday through Thursday** only.

Contact FEDEX customer service to determine the latest pickup time for your site and the scheduling deadline. Record the FEDEX Tracking number from the top of each airbill for your records and tracking purposes.

Note: A Shipping Notification should be send prior to shipping.
Electronic packaging slip must be sent to [redacted]

SHIPPING ADDRESS

Melissa Hopper/Patricia Cheung
Scientist, Pharmacyclics LLC.
995 E Arques Ave., Sunnyvale, CA94085, USA

The pharmacodynamics of ibrutinib binding to patient's cells is determined by a competitive probe assay which measures the amount of BTK that is not bound by ibrutinib. PCI-41025 is the "probe" that consists of ibrutinib linked to biotin via a long chain linker. Labeled probe will produce a signal which allows for the detection of BTK not occupied by drug. PBMC of patients is isolated pre- and post-treatment. Protein lysate is extracted from the PBMC and is subsequently analyzed on an ELISA platform by using MSD Electrochemiluminescent Detection Technology or by Western Blot. Lysate is analyzed to achieve a signal for probe and total BTK. Total BTK is determined with an anti Human BTK antibody to capture all BTK, bound and unbound, in the lysate. The percentage of BTK occupied by ibrutinib can be determined by comparing signal of probe before and after treatments normalized to total BTK.