

Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib–rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med* 2019;381:432-43. DOI: 10.1056/NEJMoa1817073

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

Note that the statistical analysis plan is integrated directly into the protocol as section 9.



Eastern Cooperative Oncology Group

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL)

STUDY CHAIR: Tait Shanafelt, M.D.
ECOG CO-CHAIR: Neil Kay, M.D.
SWOG CO-CHAIR: Susan O'Brien, M.D.
CALGB CO-CHAIR: Mark Lanasa, M.D.
NCIC CO-CHAIR:
STUDY STATISTICIAN: Victoria Wang, PhD
LEUKEMIA COMMITTEE CHAIR: Martin Tallman, M.D.
PATIENT OUTCOMES AND SURVIVORSHIP CHAIRS: Lynne Wagner, PhD; Mary Thomas, RN, MS, AOCN
PATHOLOGY CO-CHAIR: Curtis Hanson, M.D.
LABORATORY CO-CHAIR: Curtis Hanson, M.D.

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STUDY PARTICIPANTS

ECOG
SWOG
CALGB
NCIC

ACTIVATION DATE

(date)

NOTE: This study is supported by the NCI Cancer Trials Support Unit (CTSU). Institutions not aligned with ECOG will participate through the CTSU mechanism.

Table with 4 columns: Agent, IND#, NSC#, Supply. Rows include Ibrutinib, Fludarabine, Cyclophosphamide, and Rituximab.

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STUDY CHAIR

Tait Shanafelt, M.D.
Mayo Clinic
200 First Street
Rochester, MN 55902
Telephone: 507-538-0591
Fax: 507-266-4972
E-mail: Shanafelt.Tait@mayo.edu

ECOG CO-CHAIR

Neil E. Kay, M.D.
Mayo Clinic
200 First Street SW
Rochester, MN 55905
Telephone: 507-284-1961
Fax: 507-266-9277
E-mail: Kay.Neil@mayo.edu

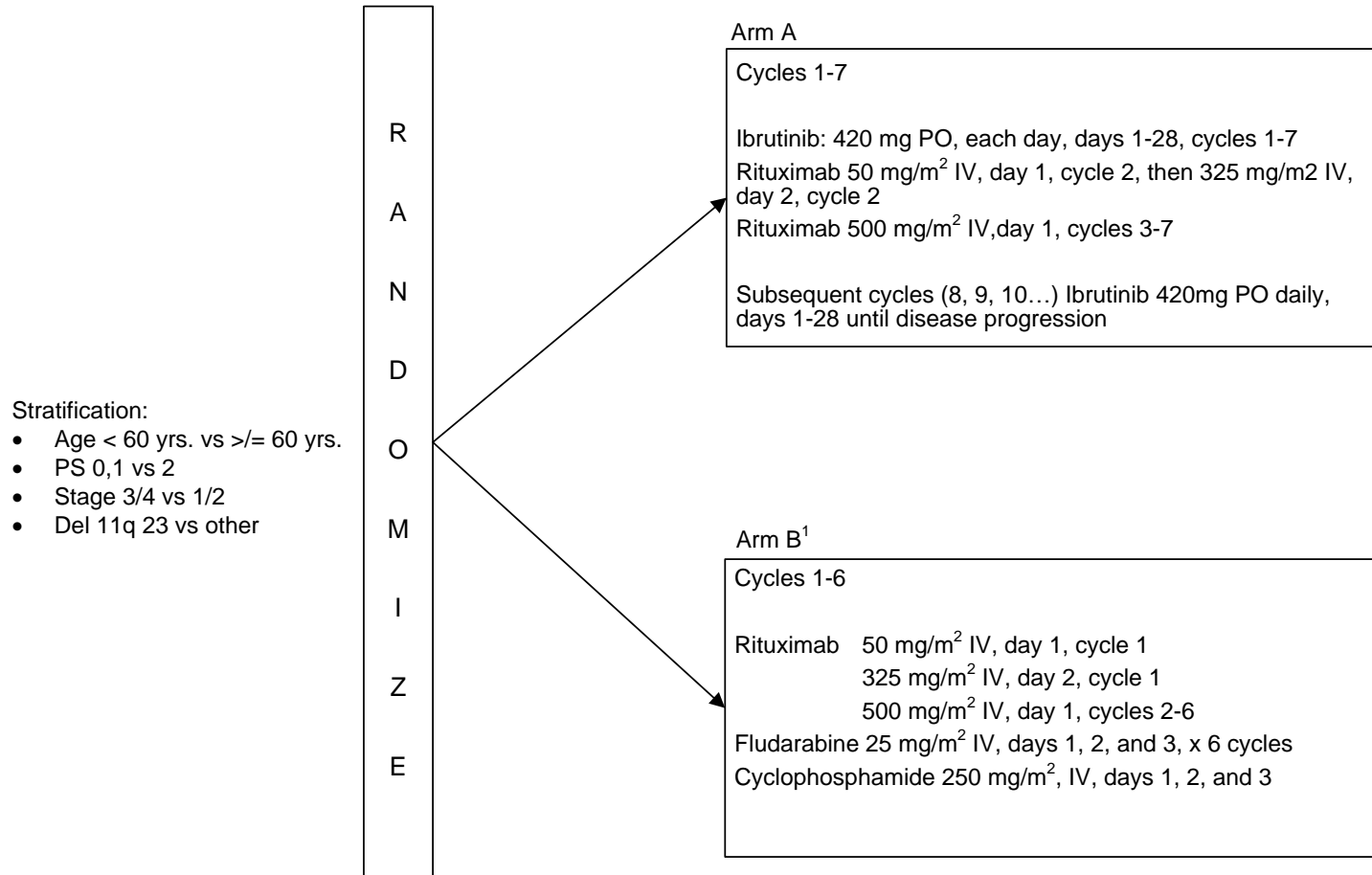
STUDY CHAIR LIAISON (SCL)

Tami Simmons
Division of Hematology
Mayo Clinic
W-10 Mayo Building
200 First Street SW
Rochester, MN 55905
Telephone: 507-284-4740
E-mail: simmons.tamera@mayo.edu

CANCER TRIALS SUPPORT UNIT (CTSUS) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	For patient enrollments:	Data collection will be performed exclusively in Medidata Rave
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSUS Fax – 215-569-0206	Please refer to the patient enrollment section for instructions on using the OPEN system.	Please refer to the Forms Completion Guidelines in the Forms Submission Schedule. Do not submit study data or forms to the CTSU Data Operations. Do not copy the CTSU on data submissions.
<p>The study protocol and all related forms and documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol.</p> <p>CTSUS sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.</p>		
<p><u>For patient eligibility or treatment-related questions</u> Contact the Study PI of the Coordinating Group.</p>		
<p><u>For questions unrelated to patient eligibility, treatment, or data submission</u> contact the CTSU Help Desk by phone or e-mail:</p> <p>CTSUS General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSUS representative.</p>		
<p><u>For detailed information on the regulatory and monitoring procedures for CTSUS sites</u> please review the CTSUS Regulatory and Monitoring Procedures policy located on the CTSUS members' website https://www.ctsu.org</p>		
<p>The CTSUS Web site is located at https://www.ctsu.org</p>		

Schema



Accrual: 519
Cycle length = 28 days

1. Arm B – Sequence of drug administration is rituximab, then fludarabine, then cyclophosphamide. See Section 5.1.3.

1. Introduction

1.1 Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is one of the most common lymphoid malignancies, accounting for ~11% of all hematologic neoplasms.¹ CLL affects approximately 100,000 individuals in the United States (~15,000 new cases/year) and is currently an incurable disease.^{1,2} While a majority of patients with CLL have early stage disease at diagnosis ~70% eventually progress to require treatment and a majority will ultimately die from CLL or CLL related complications.³⁻⁹

The last 2 decades have been a time of tremendous advances in the treatment of patients with CLL. During this interval, randomized trials have established that single agent fludarabine is superior to single agent alkylator-based approaches and demonstrated that combination of fludarabine and cyclophosphamide improves response rates and progression free survival (PFS) for younger CLL patients.¹⁰⁻¹² More recently, the addition of rituximab to purine nucleoside analogue-based chemotherapy has been shown to not only improve response rates and PFS but to also prolong overall survival in patients with CLL.

Despite the improved efficacy of CIT, only 40-45% of patients treated with these approaches currently achieve a CR and nearly all patients (including those achieving CR) eventually relapse.¹³⁻¹⁵ Although they are not curative, aggressive fludarabine based CIT regimens also result in substantial toxicity including profound immunosuppression, prolonged cytopenias (which can restrict salvage therapy options at the time of recurrence), and a 5-10% risk of therapy-related myelodysplasia (MDS).^{14, 16, 17} These toxicities are particularly problematic since nearly all CLL patients are >age 50 at diagnosis and many patients have coexistent health problems that limit their ability to receive CIT.¹³ Even among younger, fit CLL patients >25% are unable to tolerate FCR-based CIT, where previous phase 3 trial indicate that 56% of patients experience grade 3-4 myelosuppression, 25% an infectious complication, and 47% require dose reductions.¹³ Even with these extensive dose reductions, >25% of patients are unable to complete the intended 6 cycles of FCR induction.¹³ The end result is that, while FCR has been a major advance in the CLL treatment, it is associated with profound toxicity that limits the benefit of this approach for many patients.

These facts continue to foster interest in identifying novel approaches to improve both the efficacy and tolerability of CLL therapy. Although pilot studies have explored intensification approaches adding additional cytotoxic agents to CIT in an effort to improve efficacy (e.g. FCRM, CFAR, OFAR), the substantial toxicity of standard CIT renders these intensification approaches unfeasible for most CLL patients.^{18, 19}

While new combinations of existing/traditional chemotherapeutic agents may lead to incremental progress in CLL treatment, more substantive improvements will likely occur through therapeutic targeting of novel biologic pathways critical to the survival and/or chemotherapy resistance of CLL B-cells. A profound increase in the understanding of CLL B-cell biology over the last decade has identified numerous potential therapeutic targets. In this regard, interrupting survival signals mediated through the B-cell receptor appears to be one of the most promising approaches.²⁰ Multiple groups have now demonstrated single-agent

activity with a variety of compounds that interrupt B-cell receptor signaling pathway including SYK inhibitors²¹, PI3 kinase inhibitors, mTOR inhibitors, and Bruton's tyrosine kinase inhibitors^{22, 23}. Notably, these agents have generally been found to be well tolerated and to have the additional benefit of being orally administered. The activity of these targeted agents in relapsed/refractory CLL patients has created substantial interest in exploring how they may be incorporated into first-line therapy with the aim of improving efficacy and tolerability.

1.2 Ibrutinib (NSC 748645)

Ibrutinib is one of the most promising of these new compounds. Ibrutinib is an irreversible inhibitor of Bruton's tyrosine kinase (Btk), a member of the Tec family of tyrosine kinases and a protein which is over-expressed in patients with CLL. Btk is a critical protein involved in B cell development, differentiation, and signaling as well as B cell proliferation and survival.¹⁸ Inhibition of this kinase has been shown to cause modest apoptosis *in vitro*, and significantly inhibits B cell signaling both *in vitro* and *in vivo* (¹⁹ and unpublished data). The initial phase I studies examined dose escalation in various B cell malignancies. In this study, 15 patients with CLL were enrolled with objective response observed in 9/15 patients.(Fowler, ASH 2010) The drug was well tolerated at all dose levels examined, with only 5 out of 47 patients discontinuing therapy for toxicity. (Fowler, ASH 2010). A fluorescent-labeled probe was used to ensure that the doses brought forward occupied >90% of Btk,(Pollyea, ASCO 2009) and based on this study, a dose of 420 mg daily was established as a tolerable and effective dose. In an ongoing phase Ib/II study, this agent has shown extraordinary activity in 61 patients with relapsed or refractory CLL (O'Brien, ASH 2011). In patients with relapsed or refractory CLL and measurable adenopathy, the rate of lymph node shrinkage >50% is 89%. After a median follow-up of ~12 months, ORR is 68%.(O'Brien, ASH 2011). Transient lymphocytosis in this trial of Ibrutinib similar to that observed in clinical trials with the PI3 kinase delta inhibitor Cal-101 and is likely related to B-cell release from lymph node and spleen microenvironment due to disruption of homing signals or chemoattractants. Lymphocytosis with Ibrutinib agent has generally begun within the first 2 cycles, appears to resolve sooner than has been observed with Cal-101, and has resolved over time in virtually all patients. While this is currently under investigation, the magnitude and duration of lymphocytosis does not appear to be related to the depth of eventual response nor to response duration or toxicity. Response to Ibrutinib also occurs independently of high risk genomic features including IVGH mutational status and deletion(17p13.1). Studies are ongoing with this agent in both relapsed and previously untreated patients. The majority of patients in both groups remain on therapy and response over time has continued to improve as the majority of patients have had slow continued resolution of their lymphocytosis.

Thus far only 3 out of 83 patients have been removed from study for disease progression after 10-12 months follow-up. Oral Ibrutinib is well tolerated, with a very low rate of hematologic toxicity and few patients discontinuing therapy due to AE. The most common toxicities with Ibrutinib have been diarrhea, cough, fatigue, upper respiratory infection, rash, and bruising. Importantly, they do not overlap with the typical toxicities observed with CIT induction. The efficacy seen

thus far and tolerability of this agent administered continuously now to many patients for a year or more make it an ideal agent for further study.

The efficacy of Ibrutinib in combination with anti-CD20 monoclonal antibodies is also being explored in a multi-cohort phase 2 trial for patients with relapsed CLL and other B-cell malignancies at the Ohio State University. In the first cohort of 27 patients, Ibrutinib (430 mg) begins on day 1 and continues until disease progression with anti-CD20 monoclonal antibody treatment beginning month 2. All 27 patients completed the first month of therapy without a DLT. Of the 24 patients with CLL, a high rate of clinical activity has been observed and 23 patients remain on treatment (1 patient proceeded to non-ablative stem cell transplant). A second cohort of patients was accrued in whom the anti-CD20 monoclonal antibody treatment began on cycle 1 day 1 with Ibrutinib (420 mg) beginning cycle 1 day 2 (current accrual n=20). Nineteen patients completed 1 month of therapy and one patient suffered a subdural hematoma that was fatal. This patient was on warfarin and had other risk factors for developing this complication. Infusion toxicities with anti-CD20 monoclonal antibody on day 1 were manageable but in general were more severe than observed in the first cohort. A third cohort of patients where anti-CD20 monoclonal antibody is given for 8 weeks prior to beginning Ibrutinib is currently enrolling patients. Collectively, the Ohio State experience of giving Ibrutinib concurrent with anti-CD20 monoclonal antibody therapy suggests a run in with Ibrutinib for the first month followed by initiation of anti-CD20 monoclonal antibody beginning month two may be better tolerated. This schedule of administration will be pursued in this study.

1.3 Rationale

These early trials with Ibrutinib indicate that this agent is effective and well tolerated in patients with relapsed or refractory CLL and that combining Ibrutinib with anti-CD20 monoclonal antibodies is both well-tolerated and may improve efficacy. Ibrutinib has also been shown to antagonize microenvironment signals in CLL, which may make it particularly effective at clearing bone marrow disease which is a frequent site for residual disease at the completion of CIT²⁵. These characteristics, in combination with Ibrutinib's excellent tolerability profile and the fact it is an orally administered agent appear to make it ideally suited for testing as both induction therapy or as a consolidation strategy for eradicating residual disease after CIT induction.

The present trial is designed to compare targeted therapy using an oral, Bruton's tyrosine kinase inhibitor (Ibrutinib) to fludarabine-based induction (and reserve it as a salvage therapy) in younger patients (\leq age 70) with previously untreated CLL. The study employs a randomized phase III design.

1.4 Quality of Life

CLL has important impacts on patient QOL. Even though most patients with CLL are asymptomatic at the time of diagnosis and are observed for several years prior to starting treatment, the diagnosis has a substantial impact on emotional QOL even before symptoms develop.²⁶ Once patients progress to require treatment, they must deal not only with the effects of the disease on QOL but the effects of treatment.^{27, 28} Several studies suggest that QOL may decline during the active phase of fludarabine based treatment but that such therapy improves QOL over the long run by alleviating disease related symptoms.^{12, 28, 30} Not

surprisingly, these studies also provide evidence that patients with a better response to treatment have greater improvements in QOL suggesting that disease control and improvements in QOL are linked.¹² Although it is possible that agents such as Ibrutinib may improve the QOL of CLL patients receiving first-line therapy relative to fludarabine-based therapy due to their apparent favorable toxicity profile, such an advantage may be short lived if they provide less effective disease control. In addition, although the toxicity profile of Ibrutinib appears favorable relative to fludarabine-based therapy, the need for chronic indefinite administration may result in chronic side effects that ultimately erode QOL over the long run compared to a more intense but limited treatment schedule. The present trial will assess QOL of CLL patients receiving Ibrutinib and fludarabine-based therapy to explore these aspects.

While the primary QOL objective is to assess the impact of therapy on QOL between two treatment arms, it is also important to assess the impact of treatment-related toxicity on QOL during treatment. Thus we will perform QOL assessments at baseline and at two time points during treatment (3 and six months after randomization). We will also evaluate the effects of these two treatment approaches over QOL over the longer term by assessing QOL at the time of the 12 month response evaluation and then every 6 months for 2 years. While those patients assigned to the FCR arm will be off active treatment at these points, patients assigned to the experimental Ibrutinib-based treatment arm will still be taking therapy. Thus the QOL of patients at these later time points may still differ between arms even though response rates may be equivalent. Moreover, as previously stated, improved QOL may be linked to improved disease control. This study provides us the opportunity to test this hypothesis by following patients longitudinally to see if improvements in QOL are sustained for a longer period of time in the disease control phase (up to 2 years after treatment) as well as to test for long-term differences in QOL between the two groups.

2. Objectives

2.1 Primary Objectives

- 2.1.1 The primary objective for the trial is to evaluate the ability of Ibrutinib - based induction therapy to prolong progression free survival (PFS) compared to standard FCR chemoimmunotherapy for younger patients with CLL.

2.2 Secondary Objectives

- 2.2.1 Evaluate overall survival (OS) of patients based on treatment arm.
- 2.2.2 Monitor and assess toxicity of treatment with Ibrutinib-based induction relative to standard FCR chemotherapy.
- 2.2.3 To compare quality of life (QOL) in CLL patients during the first 6 months of treatment among patients receiving Ibrutinib-based induction therapy relative to standard FCR chemoimmunotherapy.
- 2.2.4 To compare QOL over the long-term in CLL patients receiving continuous therapy using Ibrutinib to that of CLL patients who completed FCR therapy.
- 2.2.5 Determine the effect of pretreatment clinical and biological characteristics (e.g. disease stage, IGHV mutation status, FISH) on clinical outcomes (e.g. complete response, PFS) of the different arms
- 2.2.6 Determine if the minimal residual disease (MRD) status as assessed by flow cytometry at different time points during and after treatment is an effective surrogate marker for prolonged PFS and overall survival.
- 2.2.7 Compare the genetic abnormalities and dynamics of intra-clonal architecture of CLL patients before and after treatment with CIT and non-CIT approaches and explore relationships with treatment resistance.
- 2.2.8 Explore the effects of FCR and Ibrutinib-based therapy on T-cell immune function
- 2.2.9 Conduct confirmatory validation genotyping of single nucleotide polymorphisms (SNPs) associated with the efficacy and toxicity of fludarabine-based therapy as in a prior ECOG GWAS analysis in the E2997 trial.
- 2.2.10 Evaluate the ability of prognostic model that incorporates clinical and biologic characters to predict a response to therapy and clinical outcome (PFS, OS)
- 2.2.11 Evaluate signaling networks downstream of the B-cell receptor in patients receiving Ibrutinib-based therapy.
- 2.2.12 Collect relapse samples to study mechanisms of resistance to both FCR and Ibrutinib-based therapy.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Diagnosis of CLL according to the NCI/IWCLL criteria or SLL according to the WHO criteria.

This includes **previous** documentation of:

- Biopsy-proven small lymphocytic lymphoma
- OR
- Diagnosis of CLL according to the NCI/IWCLL criteria² as evidenced by all of the following:
 - Peripheral blood lymphocyte count of greater than $5 \times 10^9/L$
 - Immunophenotype consistent with CLL defined as:
 - The predominant population of lymphocytes share both B-cell antigens [CD19, CD20 (typically dim expression), or CD23] as well as CD5 in the absence of other pan-T-cell markers (CD3, CD2, etc).
 - Clonality as evidenced by κ or λ light chain restriction (typically dim immunoglobulin expression)
- Negative FISH analysis for t(11;14)(IgH/CCND1) on peripheral blood or tissue biopsy (e.g. marrow aspirate) or negative immunohistochemical stains for cyclin D1 staining on involved tissue biopsy (e.g. marrow aspirate or lymph node biopsy).

NOTE: ECOG patients must be registered to E3903 (Ancillary Laboratory Protocol for the Collection of Diagnostic Material on Patients Considered for ECOG Treatment Trials for Leukemia or Related Hematologic Disorders).

- E3903 is currently not open at the CTSU. Intergroup/CTSU institutions are exempt from participating in E3903.
- _____ 3.1.2 No prior chemotherapy or monoclonal anti-body therapy for treatment of CLL or SLL
- _____ 3.1.3 Has met **at least one** of the following indications for treatment:
- Evidence of progressive marrow failure as manifested by the development of worsening anemia (Hg < 11 g/dl) and/or thrombocytopenia (Platelets < 100 x 10⁹/L)
 - Symptomatic or progressive lymphadenopathy, splenomegaly, or hepatomegaly.
 - One or more of the following disease-related symptoms:
 - Weight loss ≥10% within the previous 6 months
 - Grade 2 or 3 fatigue attributed to CLL
 - Fevers >100.5°F for 2 weeks without evidence of infection
 - Clinically significant night sweats without evidence of infection
 - Progressive lymphocytosis (not due to the effects of corticosteroids) with an increase of >50% over a two-month period or an anticipated doubling time of less than six months.
- _____ 3.1.4 Age ≥ 18 years and ≤ 70
- _____ 3.1.5 ECOG performance status between 0-2.
- _____ 3.1.6 Life expectancy of ≥ 12 months
- _____ 3.1.7 Ability to tolerate FCR based therapy
- _____ 3.1.8 No deletion of 17p13 on cytogenetic analysis by FISH
- _____ 3.1.9 The following laboratory values obtained ≤ 14 days prior to registration:
- _____ Creatinine ≤ 1.5Glomerular filtration rate (GFR)>40 mL/minute x upper limit of normal [ULN]
- _____ Total bilirubin ≤ 2.5 x ULN unless due to Gilbert's disease. For those with a total bilirubin > 2.5 x ULN, a direct bilirubin should be performed and must be < 1.5 mg/dL for Gilbert's to be diagnosed.
- _____ SGOT ≤ 2.5 x ULN
- NOTE:** If value is higher due to hepatic involvement by CLL, patient is eligible.
- _____ 3.1.10 No active hemolytic anemia requiring immunosuppressive therapy or other pharmacologic treatment. Patients who have a positive Coombs test but no evidence of hemolysis are NOT excluded from participation.
- _____ 3.1.11 No current use of corticosteroids. EXCEPTION: Low doses of steroids (<10 mg of prednisone or equivalent dose of other steroid) used for treatment of non-hematologic medical condition (e.g. chronic adrenal insufficiency) is permitted.

-
- _____ 3.1.12 No previous use of corticosteroids for autoimmune complications that have developed since the initial diagnosis of CLL. Prior use of corticosteroids for reasons other than treatment of autoimmune complications is allowed.
- _____ 3.1.13 No other active primary malignancy (other than non-melanomatous skin cancer or carcinoma in situ of the cervix) requiring treatment or limiting expected survival to ≤ 2 years.
- NOTE:** If there is a history of prior malignancy, they must not be receiving other specific treatment (other than hormonal therapy for their cancer).
- _____ 3.1.14 Able to adhere to the study visit schedule and other protocol requirements.
- _____ 3.1.15 No major surgery within the last 28 days prior to registration or minor surgery within the last 5 days.
- _____ 3.1.16 No radiation therapy ≤ 4 weeks prior to registration
- _____ 3.1.17 Patients with HIV infection may be eligible provided they meet the following criteria:
- CD4-positive cell count \geq lower limit of institutional normal
 - HIV viral load $< 10,000$ copies HIV RNA/mL (if not on anti-HIV therapy) OR < 50 copies HIV RNA/mL (if on anti-HIV therapy)
 - No evidence of hepatitis B or C infection
 - No evidence of resistant strains of HIV
 - No history of AIDS-defining condition
- _____ 3.1.18 Patients must not have any of the following conditions:
- New York Heart Association Class III or IV heart disease
 - Recent myocardial infarction (≤ 3 months)
 - Uncontrolled infection
 - Cerebral vascular accident or intracranial bleed within the last 6 months
 - Infection with known chronic, active hepatitis C.
 - Positive serology for Hepatitis B defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a Hepatitis B DNA test will be performed and, if positive the subject will be ineligible.
- _____ 3.1.19 Patients are not eligible if they require chronic use of strong or moderate CYP3A4/5 inhibitors or inducers at the time of registration (see [Appendix VIII](#)). For additional information regarding use of moderate CYP3A4/5 inhibitors see Section [8.1.12](#).
- _____ 3.1.20 Patients may not be on any other investigational agents
- _____ 3.1.21 Patients may not have received warfarin or another vitamin K antagonist in the preceding 30 days.
-

_____ 3.1.22 Women must not be pregnant or breast-feeding since this study involves an investigational agent whose genotoxic, mutagenic, and teratogenic effects on the developing fetus and newborn are unknown.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.23 Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study.

Physician Signature

Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation

4. Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at <https://www.ctsu.org>; then click on the Register tab) or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at <https://www.ctsu.org>.

Requirements for E1912 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Submitting Regulatory Documents

Before an ECOG Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. **CTSU Regulatory Transmittal Form.**
2. **Copy of IRB Informed Consent Document.**

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. **A. CTSU IRB Certification Form.**
Or
B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
Or
C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- **Indicate all sites approved for the protocol under an assurance number.**
- **OHRP assurance number of reviewing IRB**
- **Full protocol title and number**
- **Version Date**
- **Type of review (full board vs. expedited)**
- **Date of review.**
- **Signature of IRB official**

The CTSU encourages you to go to the following CTSU RSS webpage so that more information on RSS2.0 as well as the submission forms can be accessed. Log in to <http://www.ctsu.org> and click on the Regulatory tab to access the RSS webpage. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com. Monday through Friday, 9:00am - 8:30pm.

Patients must not start protocol treatment prior to registration.

Treatment should start within 14 working days after registration.

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the database. OPEN can be accessed at <https://open.ctsu.org> or from the OPEN tab on the CTSU members' side of the website at <https://www.ctsu.org>.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria has been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site

and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at <https://www.ctsu.org> or at <https://open.ctsu.org>. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

The following information will be requested

4.1 Protocol Number

4.2 Investigator Identification

- 4.2.1 Institution and affiliate name (Institution CTEP ID)
- 4.2.2 Investigator's name (NCI number)
- 4.2.3 Cooperative Group Credit
- 4.2.4 Credit Investigator
- 4.2.5 Protocol specific contact information

4.3 Patient Identification

- 4.3.1 Patient's initials (first and last)
- 4.3.2 Patient's Hospital ID and/or Social Security number
- 4.3.3 Patient demographics
 - 4.3.3.1 Gender
 - 4.3.3.2 Birth date
 - 4.3.3.3 Race
 - 4.3.3.4 Ethnicity
 - 4.3.3.5 Nine-digit ZIP code
 - 4.3.3.6 Method of payment
 - 4.3.3.7 Country of residence

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section [3](#).

4.5 Stratification Factors:

- 4.5.1 Age: < 60 years vs. ≥ 60 years
- 4.5.2 PS 0,1 vs 2
- 4.5.3 Disease stage: 3/4 vs. 1/2
- 4.5.4 Baseline cytogenetic abnormalities on FISH: deletion 11q23 vs. other

4.6 Additional Requirements

- 4.6.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG Coordinating Center.

NOTE: ECOG Institutions: Patients must be registered to E3903.

- 4.6.2 Bone marrow sections/slides must be submitted for central review as outlined in Section [10](#).

- 4.6.3 Baseline peripheral blood and smears must be submitted for review as outlined in Section [10](#).

NOTE: ECOG Institutions: Patients must be registered to E3903, Ancillary Laboratory Protocol for the Collection of Diagnostic Material on Patients Considered for ECOG Treatment Trials for Leukemia or Related Hematologic Disorders.

The E3903 ECOG sequence number must be indicated at time of randomization to E1912.

E3903 is currently not open at the CTSU. Therefore, Intergroup/CTSU institutions are exempt from participating in E3903.

- 4.6.4 Peripheral blood and buccal cells should be submitted for correlative studies and/or banking as outlined in Section [10](#), per patient consent.

NOTE: ECOG requires that biological samples submitted from patients participating in E1912 be entered and tracked via the on-line ECOG Sample Tracking System (STS) (see Section [10.4](#)). Any case reimbursements associated with sample submissions will not be captured if samples are not logged into STS.

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG Coordinating Center regarding logistics for submission of fresh samples.

- 4.6.5 Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS after IRB approval is obtained. To access iMedidata/Rave the site user must have an active CTEP IAM account (<https://eapps-ctep.nci.nih.gov/iam>). In addition, site users that are a member of ECOG must have the mapped ECOG roles or explicit Rave roles (Rave CRA, Read-Only, Site Investigator) in RSS at the enrolling site. Site users that are not members of ECOG must have the Rave roles on the CTSU roster at the enrolling sites. The Site Administrator or Data Administrator at the enrolling site may assign the appropriate roles from the Site Roles tab on the CTSU website.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent study invitation e-mail from iMedidata. To accept the invitation, site users

must log into the Select Login (<https://login.imedidata.com/selectlogin>) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at <http://www.ctsu.org/RAVE/> or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctscontact@westat.com.

4.7 Investigational Brochure

Ibrutinib is an INVESTIGATIONAL AGENT (IND# 117241). A copy of the Investigator's Brochure (IB) can be obtained by calling the Pharmaceutical Management Branch at the NCI (240-276-6575) or via email request to ibcoordinator@mail.nih.gov.

NOTE: Please have your investigator's NCI # handy. The IB provides relevant and current scientific information about the investigational product. Please submit the IB to your IRB/EC according to GCP regulations. The IB and any correspondence to the IRB should be kept in the study files of E1912.

4.8 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E1912 Forms Completion Guidelines. Document the reason for not starting protocol treatment on the Off Treatment form. Also report the date and type of the first non-protocol treatment that the patient receives.

5. Treatment Plan

5.1 Administration Schedule

All questions regarding treatment and dose modifications should be directed to the ECOG Study Chair.

All drugs that will be administered according to weight should be dosed according to actual body weight. There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by (1) the patient's BSA as calculated from actual weight or (2) actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese patients on this protocol.

Intravenous medications in both study arms may be administered via the following methods: peripheral IV, Port-a-cath, central line, PIC, or Hickman.

NOTE: BSA will be calculated prior to each cycle based on body weight at the start of that cycle. Accordingly, the dose of drugs based on BSA (e.g. fludarabine, cyclophosphamide, rituximab) may vary slightly cycle by cycle due to fluctuations in body weight. Changes to doses cycle by cycle are allowed but not required unless calculated dose changes by greater than 10%.

5.1.1 ARM A: Ibrutinib with Rituximab

Therapy will consist of daily oral Ibrutinib in combination with rituximab. For the first month of therapy patients will receive Ibrutinib alone. Beginning with the second cycle, patients will receive rituximab. Since the rituximab begins in cycle 2 rather than cycle 1, patients will receive rituximab during cycles 2-7 so that they receive an identical cumulative dose of rituximab to arm B. After completion of cycle 7, patients will continue on daily oral Ibrutinib until disease progression. Patients will be assessed with physical examination, CBC, and chemistries prior to cycle 1-7 as per Section [7.1](#). Following day 1 of cycle 7, patients will be seen every 90 days (+/-7 days).

NOTE: Ibrutinib should be taken with 8 ounces (approximately 240 ml) of water. The capsules are to be swallowed intact, not less than 30 minutes before or 2 hours after a meal. Patients should avoid consuming food and beverages containing grapefruit juice or Seville oranges for the duration of the study due to CYP3A4/5 inhibition.

NOTE: Doses are to be taken at about the same time each day. If an ibrutinib dose is missed, it should be made up as soon as possible on the same day with a return to the normal schedule the following day.

5.1.1.1 Drugs

Cycle 1:

- Ibrutinib 420 mg orally once per day for 28 days (+/- 4 days)
- Patients will be seen every 28 days (+/- 4 days)

NOTE: Patients with a baseline platelet counts below $20 \times 10^9/L$ should receive platelet transfusion prior to starting Ibrutinib therapy. As noted in Section 7.0, patients whose baseline platelet count is below $20 \times 10^9/L$ should have repeat CBC on day 3.

Cycles 2-7:

- Ibrutinib 420 mg orally once per day for 28 days (+/- 4 days)
- Rituximab, 50 mg/m² IV on day 1 of Cycle 2, and 325 mg/m² on day 2 of Cycle 2, then 500 mg/m² on day 1 of Cycles 3-7.

NOTE: Patients with a baseline platelet counts below $20 \times 10^9/L$ should receive platelet transfusion prior cycle 2, day 1 rituximab therapy. As treatment with anti-CD20 monoclonal antibodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts $< 50 \times 10^9/L$, prior to receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.

- Repeat cycles every 28 days (+/- 4 days) for a total of 6 cycles

After cycle 7

- Ibrutinib 420 mg orally once per day continuously until disease progression.
- During this phase patients will be seen every 90 days (+/-7 days)

5.1.1.2 Unless otherwise indicated, premedication prior to all doses of rituximab (Cycles 1-6) will include the following:

- Hydrocortisone 100 mg IV (or equivalent dose of other corticosteroid) should be administered before the first and second doses of rituximab during Cycle 1 of therapy. Thereafter, it should only be administered if patients have infusion reactions or nausea that is not controlled by alternative anti-emetics.
- Diphenhydramine 50 mg IV or PO and acetaminophen 650 mg PO should be administered 30 minutes prior to rituximab to reduce infusion reactions. Patients with allergic reactions to diphenhydramine may receive an

alternative anti-histamine or have anti-histamines held at the discretion of the treating physician.

- 5.1.1.3 The following premedication will be administered prior to Cycles 1-3:
- All patients will be given PO allopurinol 300 mg/day from day 1 to day 14 (a total of 14 days) of Cycles 1 and 2 unless they are allergic. Treatment with allopurinol may continue beyond 14 days during Cycles 1 and 2 at the discretion of the treating physician. Use of allopurinol with subsequent cycles will be at the discretion of the treating physician.
 - Use of antiemetic therapy will be left to the discretion of the treating physician
- 5.1.1.4 Ibrutinib 420 mg orally once per day on days 1-28 days of cycles 1-7. After the end of cycle 7, patients will remain on Ibrutinib 420 mg orally once per day until disease progression. *During this phase patients will be seen every 90 days (+/-7 days)*
- 5.1.1.5 Rituximab administration:
- On day 1 Cycle 2:** rituximab 50 mg/m² mg will be administered IV over a period of 4 hours. To determine the hourly rate of infusion, divide the total volume of rituximab solution by 4 and administer at this rate, without escalation, for 4 hours. Shortness of breath, rigors and other infusion-related toxicities have been noted more frequently during the first infusion and in patients with high leukocyte counts. Vital signs are recommended to be measured every 15 minutes for the first 2 hours with the first dose of rituximab.
- On day 2 of Cycle 2:** rituximab 325 mg/m² will be administered IV. Rituximab can usually be initiated at 50 mg/hr. If hypersensitivity or infusion related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. Close observation for infusion-related toxicities should occur throughout the infusion, particularly with each dose escalation.
- On day 1 of cycles 3-7:** rituximab 500 mg/m² will be administered IV. Rituximab can usually be initiated at 50 mg/hr. If hypersensitivity or infusion related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. Close observation for infusion-related toxicities should occur throughout the infusion, particularly with each dose escalation.
- Rituximab Infusion reactions:**
- Shortness of breath, rigors and other infusion-related toxicities have been noted more frequently in patients

with high leukocyte counts and during the first several treatments. Close observation for these potential toxicities should occur. The treatment area should be sufficiently prepared to allow easy access to supportive care medications and measures, such as meperidine for IV push, oxygen supplementation and nebulized albuterol, warm blankets, IV fluid for bolus, and access to crash cart.

- If infusion reactions occur, infusions should be stopped until infusion-related symptoms resolve, and then resumed at a 50% slower rate. Contact the ECOG Study Chair or ECOG Committee chair with any questions.
- If transient bronchospasm occurs, rituximab administration should be interrupted. If these symptoms persist, albuterol (or other B₂ agonist) by inhalation and additional hydrocortisone should be administered at the discretion of the treating physician.
- In patients with high leukocyte counts, close observation for potential toxicities should occur. If marked reduction in circulating lymphocytes is noted, close attention to the possibility of acute tumor lysis syndrome should occur.

5.1.2 As treatment with anti-CD20 monoclonal anti-bodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts $< 50 \times 10^9/L$ prior to receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary. Criteria for converting patients who do not respond to Ibrutinib therapy

At the end of cycle 4, patients will be assessed with physical examination and CBC as per Section [7.1](#). Patients with progressive disease or those who have not experienced at least a $\geq 50\%$ reduction in lymphadenopathy will be considered to have failed Ibrutinib based therapy. These patients will be considered a treatment failure and will discontinue Ibrutinib-based therapy. If deemed appropriate by their treating physician, patients may receive salvage therapy (off protocol) with FCR for 6 cycles using the schedule outlined for Arm B.

NOTE: It should be noted that it is common for CLL patients treated with Ibrutinib to experience a transient increase in lymphocytosis due to redistribution of lymphocytes from the lymph nodes and spleen to the peripheral blood circulation. This lymphocytosis is NOT a marker of disease progression or Richter's transformation and typically resolves over several months. For this reason, no patient on Ibrutinib will be considered to have disease progression based on an increased absolute lymphocyte count that occurs during the first several months of Ibrutinib based treatment. See protocol Section [5.1.2](#). Questions regarding an increase in

the absolute lymphocyte count after initiation of Ibrutinib-based therapy should be discussed with the study PI.

5.1.3 ARM B: FCR for 6 cycles

Therapy will consist of 6 28-day cycles of fludarabine, cyclophosphamide, and rituximab. The sequence of drug administration is as follows: (1) rituximab, (2) fludarabine, (3) CTX. Patients will be assessed with physical examination, CBC, and chemistries prior to cycle 1-6 as per Section 7.1. Patients will also be evaluated at the end of cycle 6, 90 days (+/-7 days) after the end of cycle 6 and then 12 months post registration as outlined in Section 7.1.

5.1.3.1 Drugs

Cycles 1 – 6:

- Rituximab, 50 mg/m² IV on day 1 and 325 mg/m² on day 2 of Cycle 1 and 500 mg/m² on day 1 of Cycles 2-6.
- Fludarabine 25 mg/m², IV, days 1, 2, 3
- Cyclophosphamide 250 mg/m², IV, days 1, 2, 3
- Repeat cycles every 28 days (+/- 4 days) for a total of 6 cycles.

NOTE: Patients with a pre-treatment platelet counts below $20 \times 10^9/L$ should receive platelet transfusion prior cycle 1, day 1 rituximab therapy. As noted in Section 7.0, patients whose pre-treatment platelet count is below $20 \times 10^9/L$ should have repeat CBC on day 3.

As treatment with anti-CD20 monoclonal antibodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts $< 50 \times 10^9/L$ prior to receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.

5.1.3.2 Unless otherwise indicated, premedication prior to all doses of rituximab (Cycles 1-6) will include the following:

- Hydrocortisone 100 mg IV (or equivalent dose of other corticosteroid) should be administered before the first and second doses of rituximab during Cycle 1 of therapy. Thereafter, it should only be administered if patients have infusion reactions or nausea that is not controlled by alternative anti-emetics.
- Diphenhydramine 50 mg IV or PO and acetaminophen 650 mg PO should be administered 30 minutes prior to rituximab to reduce infusion reactions. Patients with allergic reactions to diphenhydramine may receive an

alternative anti-histamine or have anti-histamines held at the discretion of the treating physician.

5.1.3.3 The following premedication will be administered prior to Cycles 1-6:

- All patients will be given PO allopurinol 300 mg/day from day 1 to day 14 (a total of 14 days) of Cycle 1 unless they are allergic. Treatment with allopurinol may continue beyond 14 days at the discretion of the treating physician. Use of allopurinol with subsequent cycles will be at the discretion of the treating physician.
- Antiemetic medications such as Kytril 1 mg PO (or substitute) should be given thirty minutes to 1 hour prior to chemotherapy (fludarabine and/or cyclophosphamide). Additional prophylactic antiemetic therapy will be left to the discretion of the treating physician
- All patients should be well hydrated before each cycle of therapy. Patients should be encouraged to drink fluids the night before treatment and will receive approximately 500 to 1000 mL of IV hydration over 1 hour prior to chemotherapy on days they receive fludarabine and cyclophosphamide.
- On Day 2 of Cycle 1 only, CBC with differential, Ca⁺⁺, PO₄, LDH, uric acid, electrolytes, BUN, and creatinine are required to assess for tumor lysis syndrome prior to the second fludarabine dose (see Section [7.1](#)).

5.1.3.4 Rituximab administration:

On day 1 Cycle 1: rituximab 50 mg/m² mg will be administered IV over a period of 4 hours. To determine the hourly rate of infusion, divide the total volume of rituximab solution by 4 and administer at this rate, without escalation, for 4 hours. Shortness of breath, rigors and other infusion-related toxicities have been noted more frequently during the first infusion and in patients with high leukocyte counts. Vital signs are recommended to be measured every 15 minutes for the first 2 hours with the first dose of rituximab.

On day 2 of Cycle 1: rituximab 325 mg/m² will be administered IV. Rituximab can usually be initiated at 50 mg/hr. If hypersensitivity or infusion related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. Close observation for infusion-related toxicities should occur throughout the infusion, particularly with each dose escalation.

On day 1 of cycles 2-6: rituximab 500 mg/m² will be administered IV. Rituximab can usually be initiated at 50 mg/hr. If hypersensitivity or infusion related events do not occur, escalate the infusion rate in 50 mg/hr increments

every 30 minutes to a maximum of 400 mg/hr. Close observation for infusion-related toxicities should occur throughout the infusion, particularly with each dose escalation.

Rituximab Infusion reactions:

- Shortness of breath, rigors and other infusion-related toxicities have been noted more frequently in patients with high leukocyte counts and during the first several treatments. Close observation for these potential toxicities should occur. The treatment area should be sufficiently prepared to allow easy access to supportive care medications and measures, such as meperidine for IV push, oxygen supplementation and nebulized albuterol, warm blankets, IV fluid for bolus, and access to crash cart.
- If infusion reactions occur, infusions should be stopped until infusion-related symptoms resolve, and then resumed at a 50% slower rate. Contact the ECOG Study Chair or ECOG Committee chair with any questions.
- If transient bronchospasm occurs, rituximab administration should be interrupted. If these symptoms persist, administration of albuterol (or other B2 agonist) by inhalation and additional hydrocortisone should be administered at the discretion of the treating physician.
- In patients with high leukocyte counts, close observation for potential toxicities should occur. If marked reduction in circulating lymphocytes is noted, close attention to the possibility of acute tumor lysis syndrome should occur.
- As treatment with anti-CD20 monoclonal anti-bodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts $< 50 \times 10^9/L$ prior to receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.

5.1.3.5 Fludarabine monophosphate 25 mg/m²/day IV over 30 minutes on days 1-3 of Cycles 1-6.

(In Canada, it is permissible to substitute fludarabine monophosphate 40 mg/m²/day orally on days 1-6 of each cycle.

5.1.3.6 Cyclophosphamide 250 mg/m²/day IV over 30 minutes on days 1-3 of Cycles 1-6.

5.1.3.6 Criteria for converting patients who do not respond to FCR induction to Ibrutinib

Patients will be assessed with physical examination and CBC prior to each cycle as per Section 7.1. Patients with progressive disease (see Section 6.1.3) will be considered to have failed FCR-based therapy. These patients will be considered a treatment failure for the primary analysis and, if deemed appropriate by their treating physician, may receive salvage therapy (non-protocol) with Ibrutinib 420 mg orally once per day.

Patients will be seen every 28 days (+/- 7 days) for the first 6 months of treatment with Ibrutinib at which point the frequency of follow-up can be spaced to every 90 days (+/- 7 days) at the discretion of the treating physician

5.1.3.7 Patients who relapse after FCR

After they complete induction therapy, patients responding to FCR will be followed according as per Section 7.1. The criteria for progressive disease during follow-up are defined in Section 6.1.3. Many patients with progressive disease are asymptomatic and can be observed until they experience:

- Evidence of progressive marrow failure as manifested by the development of worsening anemia (Hgb < 11 g/dl) and/or thrombocytopenia (Platelets < 100 x 10⁹/L)
- Symptomatic or progressive lymphadenopathy, splenomegaly, or hepatomegaly.
- One or more of the following disease-related symptoms:
 - Weight loss > 10% within the previous 6 months
 - Grade 2 or 3 fatigue attributed to CLL
 - Fevers > 100.5°F for 2 weeks without evidence of infection
 - Clinically significant night sweats without evidence of infection

Patients fulfilling the criteria for progressive disease (Section 6.1.3) and in need of salvage therapy as determined by the treating physician may receive salvage therapy (non-protocol) with Ibrutinib 420 mg orally once per day if deemed appropriate by the treating physician. Patients will be seen every 28 days (+/- 7 days) for the first 6 months of treatment with Ibrutinib at which point the frequency of follow-up can be spaced to every 90 days (+/- 7 days) at the discretion of the treating physician.

5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the

patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting:** Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave. On this protocol, all adverse events, of any grade, regardless of attribution to study treatment, will be recorded on the *E1912 Adverse Event Form*.
- **Expedited reporting:** In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is clearly NOT related to treatment
Unlikely	The AE is doubtfully related to treatment
Possible	The AE may be related to treatment
Probably	The AE is likely related to treatment
Definite	The AE is clearly related to treatment

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains list of events that are protocol specific exceptions to expedited reporting. AEs listed on the SPEER should be reported expeditiously via AdEERS **ONLY if they exceed the grade listed in parentheses next to the event.**

5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at <http://ctep.cancer.gov>. An AdEERS report must be submitted electronically to ECOG and the appropriate regulatory agencies via the AdEERS Web-based application located at <http://ctep.cancer.gov>.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG (617-632-3610) for Arms A and B
- the NCI (301-897-7497) for Arm A
- the FDA (800-332-1088) Arm B

An electronic report **MUST** be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation (for Arms A and B) must be uploaded to the Supplemental Data Folder in medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 230-0159) for Arm A and the FDA (800-332-0178) for Arm B in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the AdEERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457 or 301-840-8202.

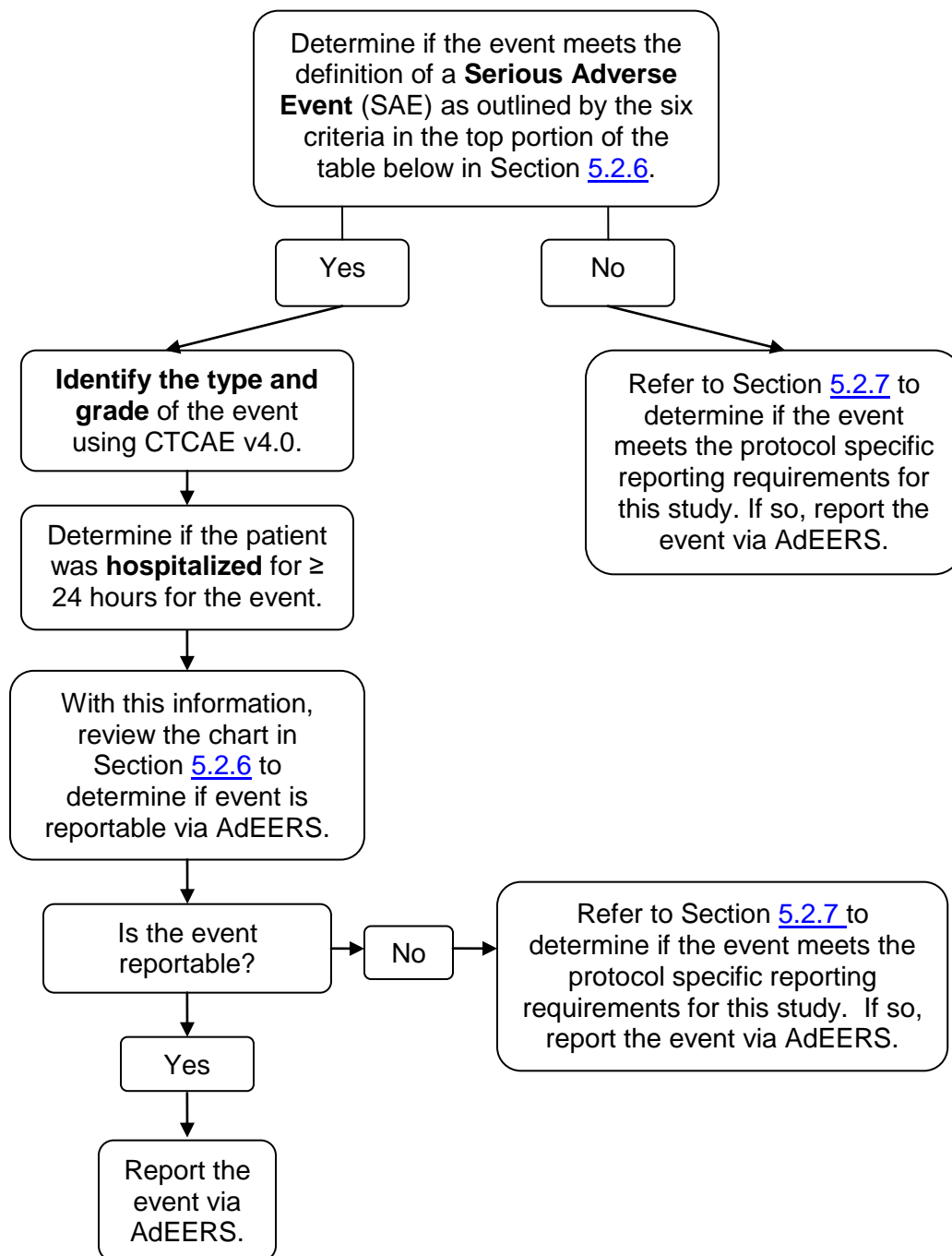
5.2.4 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. \geq 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol E1912 and outline the specific expedited adverse event reporting requirements for study E1912.

5.2.5 Steps to determine if an adverse event is to be reported in an expedited manner – Arm A

5.2.5.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).

5.2.5.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section [5.2.6](#), AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via AdEERS even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.2.6 Expedited Reporting Requirements for Arm A on protocol E1912

Investigational Agents: Ibrutinib

Commercial Agents: Rituximab

Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of the Investigational Agent/Intervention.¹

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

<p>FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)</p> <p>NOTE: Investigators MUST immediately report to the sponsor (NCI) ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)</p> <p>An adverse event is considered serious if it results in ANY of the following outcomes:</p> <ol style="list-style-type: none"> 1. Death 2. A life-threatening adverse event 3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5. A congenital anomaly/birth defect. 6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). 				
<p>ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.</p>				
Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days		
<p>NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.</p> <p>Expedited AE reporting timelines are defined as:</p> <ul style="list-style-type: none"> • “24-Hour; 5 Calendar Days” – The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report. • “10 Calendar Days” – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE. 				
<p>¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:</p> <p>Expedited 24-hour notification followed by complete report within 5 calendar days for:</p> <ul style="list-style-type: none"> • All Grade 4, and Grade 5 AEs <p>Expedited 10 calendar day reports for:</p> <ul style="list-style-type: none"> • Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization • Grade 3 adverse events 				

5.2.7 Additional instructions, requirements and exceptions for protocol E1912 – Arm A

Additional Instructions:

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via AdEERS, please contact the NCI Medical Help Desk at 301-897-7497 or adeersmd@tech-res.com. This will need to be discussed on a case by case basis.

E1912 additional expedited reporting requirements:**Pregnancy**

- Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the subject is on Ibrutinib, or within 28 days of the subject's last dose of Ibrutinib, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via AdEERS within 24 hours of the Investigator's knowledge.

Please refer to [Appendix IX](#) for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

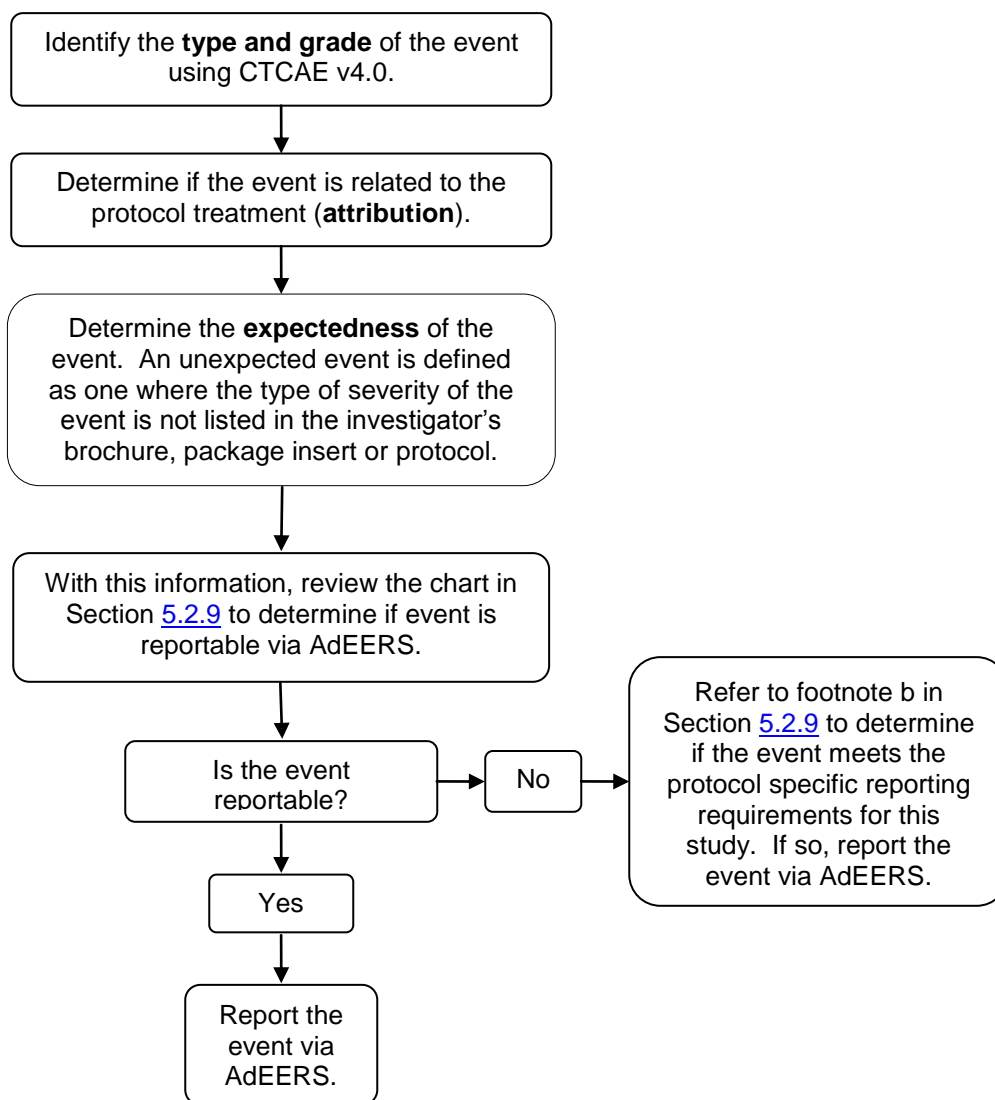
Other Adverse Events:

- Any \geq grade 3 occurrence of the following events must be reported via AdEERS regardless whether or not the patient was hospitalized. Report the event within the timeframes outlined in the chart in Section [5.2.6](#).
 - Diarrhea/Nausea/Vomiting
 - Fatigue
 - Febrile Neutropenia
 - Fever
 - Headache
 - Hematuria
 - Infusion related reaction
 - Intracranial hemorrhage
 - Lower or upper gastrointestinal hemorrhage
 - Lung infection
 - Myalgia
 - Rash maculo-papular
 - Sepsis
 - Upper respiratory infection

E1912 specific expedited reporting exceptions:

The adverse events listed on the SPEER should be reported expeditiously via AdEERS **ONLY** if they exceed the grade listed in parentheses next to the event. If the event being reported equals or is less than the grade listed in the parentheses, the event does not require reporting via AdEERS.

5.2.8 Steps to determine if an event is to be reported in an expedited manner – Arm B



5.2.9 Expedited Reporting Requirements for Arm B on protocol E1912
Commercial Agents: Fludarabine, Cyclophosphamide, and Rituximab

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only					
Attribution	Grade 4		Grade 5 ^a		ECOG and Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	
7 Calendar Days: Indicates a full AdEERS report is to be submitted within 7 calendar days of learning of the event.					
<p>a This includes all deaths within 30 days of the last dose of treatment regardless of attribution. NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.</p> <p>b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:</p> <p>Serious Events: Any event following treatment that results in <i>persistent or significant disabilities/incapacities, congenital anomalies, or birth defects</i> must be reported via AdEERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via AdEERS, please contact the NCI AdEERS Help Desk at 301-897-7497.</p>					

5.2.10 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by ECOG MUST be submitted to BOTH the NCI and ECOG.

Adverse events determined to be reportable via AdEERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.11 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
 1. Complete a Second Primary Form in Medidata Rave within 14 days.
 2. Upload a copy of the pathology report to ECOG via Medidata Rave confirming the diagnosis.

3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
 1. Complete a Second Primary Form in Medidata Rave within 14 days.
 2. Report the diagnosis via AdEERS at <http://ctep.cancer.gov>
 - *Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy*
 3. Upload a copy of the pathology report to ECOG via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
 4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG Second Primary Form and the AdEERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG Second Primary Form must be submitted for the most recent trial. ECOG must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via AdEERS or by the ECOG Second Primary Form.

5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for PCI-32765 (Ibrutinib, NSC 748645)

5.3.1 The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeg_guidelines.pdf for further clarification. Frequency is provided based on 392 patients. Below is the CAEPR for PCI-32765 (ibrutinib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, February 28, 2013¹

Adverse Events with Possible Relationship to PCI-32765 (ibrutinib) (CTCAE 4.0 Term) [n= 392]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		<i>Anemia (Gr 2)</i>
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea			<i>Diarrhea (Gr 2)</i>
	Dry mouth		
	Dyspepsia		
	Flatulence		
	Mucositis oral		
	Nausea		<i>Nausea (Gr 2)</i>
	Vomiting		<i>Vomiting (Gr 2)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
	Fatigue		<i>Fatigue (Gr 2)</i>
	Fever		
INFECTIONS AND INFESTATIONS			
	Infection ²		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		

INVESTIGATIONS		
	Neutrophil count decreased	
	Platelet count decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hyperuricemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)	
	Myalgia	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Pruritus	
	Purpura	
	Rash maculo-papular	Rash maculo-papular (Gr 2)

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

²Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

³Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

Also reported on PCI-32765 (ibrutinib) trials but with the relationship to PCI-32765 (ibrutinib) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Hemolysis; Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Atrioventricular block first degree; Cardiac disorders - Other (bundle branch block left); Cardiac disorders - Other (extrasystoles); Heart failure; Sinus bradycardia

EAR AND LABYRINTH DISORDERS - Ear pain

EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Eye disorders - Other (eye discharge); Eye disorders - Other (macular edema); Eye disorders - Other (ocular hyperemia); Eye disorders - Other (retinal hemorrhage); Eye disorders - Other (visual acuity reduced); Eye pain; Floaters; Glaucoma; Keratitis; Photophobia; Watery eyes

GASTROINTESTINAL DISORDERS - Abdominal distension; Colitis; Enterocolitis; Esophagitis; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gingival edema); Gastrointestinal disorders - Other (hypoesthesia oral); Gastrointestinal disorders - Other (irritable bowel syndrome); Gastrointestinal disorders - Other (tongue discoloration); Gastrointestinal hemorrhage³; Oral dysesthesia; Oral pain; Toothache

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (early satiety); General disorders and administration site conditions - Other (sensation of foreign body); General disorders and administration site conditions - Other (temperature intolerance); Infusion related reaction; Injection site reaction; Malaise; Non-cardiac chest pain; Pain

IMMUNE SYSTEM DISORDERS - Allergic reaction

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (excoriation)

INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (blood urea increased); Investigations - Other (cardiac murmur); Investigations - Other (pancytopenia); Lymphocyte count decreased; Weight gain; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (cachexia); Metabolism and nutrition disorders - Other (fluid retention); Metabolism and nutrition disorders - Other (hyperphosphatemia); Metabolism and nutrition disorders - Other (hypoproteinemia); Metabolism and nutrition disorders - Other (lactose intolerance); Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Generalized muscle weakness; Joint range of motion decreased; Musculoskeletal and connective tissue disorder - Other (groin pain); Musculoskeletal and connective tissue disorder - Other (medial tibial stress syndrome); Musculoskeletal and connective tissue disorder - Other (muscle rigidity); Musculoskeletal and connective tissue disorder - Other (pain in jaw); Neck pain; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (benign neoplasm of skin)

NERVOUS SYSTEM DISORDERS - Dysgeusia; Lethargy; Memory impairment; Nervous system disorders - Other (mental impairment); Nervous system disorders - Other (parosmia); Paresthesia; Peripheral sensory neuropathy; Sinus pain; Somnolence; Stroke; Syncope

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Insomnia; Restlessness

RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Renal and urinary disorders - Other (calculus bladder); Renal and urinary disorders - Other (dysuria); Renal and urinary disorders - Other (polyuria); Urinary frequency; Urinary retention; Urine discoloration

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Dyspareunia; Reproductive system and breast disorders - Other (hematospermia); Reproductive system and breast disorders - Other (vulvovaginal dryness); Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Epistaxis; Hiccups; Laryngeal inflammation; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Productive cough; Respiratory, thoracic and mediastinal disorders - Other (aveolitis allergic); Respiratory, thoracic and mediastinal disorders - Other (nasal ulcer); Sinus disorder; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Nail discoloration; Periorbital edema; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (blood blister); Skin and subcutaneous tissue disorders - Other (onychoclasia); Skin hyperpigmentation; Skin ulceration; Urticaria

VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension; Vascular disorders - Other (peripheral coldness)

NOTE: PCI-32765 (ibrutinib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.4 Dose Modifications and Management of Toxicity

Should unanticipated circumstances arise that might require minor variances from the prescribed dosing and schedule of the protocol therapy or recommended supportive care in order to ensure safety and allow patients to continue to receive treatment on study, the ECOG Study Chair should be contacted in advance for discussion and approval.

NOTE: Ibrutinib to be held in the event of major and minor surgeries: major surgeries: Hold ibrutinib for 7 days prior to and seven days after major surgeries. Minor surgeries: Hold Ibrutinib for 3 days prior and 3 days after minor surgeries.

5.4.1 Assessment of Toxicity

- An evaluation of potential treatment-induced toxicity in patients with CLL can be difficult. Moreover, some conventional criteria are not applicable to studies involving patients with hematologic malignancies in general, and CLL in particular. An example is hematologic toxicity: patients with advanced CLL may exhibit a deterioration in blood counts which may represent either treatment-related toxicity or progressive bone marrow failure from disease itself.
- **Toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 with the exception of hematologic toxicity. Grading Of Hematologic Adverse Events In This Protocol Will Be Performed As Detailed In [Appendix VI](#).**
- All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (<http://ctep.cancer.gov>).
- If the following signs and symptoms are medically manageable, they are not to be a consideration with respect to a patient's dosing or continuation in the study: nausea/vomiting, diarrhea, drug-related fever or chills, and hair loss.

5.4.2 Fludarabine and Cyclophosphamide Dose Levels for Hematologic Dose Modifications Arm B.

NOTE: Patients who require a dose reduction during a given cycle will remain at that dose for future cycles and will not be re-escalated to higher dose levels

If the modifications below indicate that either Fludarabine or Cyclophosphamide should be held, all drugs in the cycle should be held (e.g. the entire cycle delayed) until patient fulfills the indicated criteria for retreatment. Accordingly, there will not be any "missed" doses of medication.

There are no dose modifications for rituximab. If rituximab needs to be held, patients can continue to receive other treatment as prescribed by their assigned arm.

Dose Level	IV Fludarabine Dose Level	Oral Fludarabine Dose Level (Canada Only)	Cyclophosphamide Dose Level
0 (Starting Level)	25 mg/m ² /day	40 mg/m ² /day	250 mg/m ² /day
-1	18.75 mg/m ² /day	30 mg/m ² /day	200 mg/m ² /day
-2	12.5 mg/m ² /day	20 mg/m ² /day	150/m ² /day

5.4.3 Dose Modifications for Neutropenia

Neutrophil growth factors are permitted per American Society of Clinical Oncology (ASCO) guidelines (see Section [5.5.3](#)).

- **Arm A**

For Grade 4 neutropenia (ANC < 0.5 x 10⁹/L [ie, < 500/mL]) lasting > 7 days, follow the actions outlined in the table:

Occurrence	Action
1 st	Hold Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level (420 mg daily)
2 nd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (280 mg daily)
3 rd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (140 mg daily)
4 th	Discontinue Ibrutinib

Ibrutinib may be held for toxicity considerations for a maximum of 28 consecutive days. Study medication should be discontinued permanently in the event of a toxicity lasting more than 28 days. If Ibrutinib is interrupted for a reason other than toxicity (e.g. unrelated illness) it must be restarted within 60 days. If interrupted for more than 60 days, study medication should be discontinued permanently.

Patients who require a dose reduction during a given cycle will remain at that dose for future cycles and will not be re-escalated to higher dose levels.

In patients whose baseline (i.e., prior to starting protocol therapy) ANC is < 1000/μL, the above Ibrutinib dose modifications, if required, would not be applied until Cycle 3.

- **Arm B**

ANC must be ≥ 1000/μL on day 1 of a cycle. For ANC < 1000/μL, hold fludarabine and cyclophosphamide until ANC ≥ 1000/μL, then resume both at one dose level lower than previous dose (see table in Section [5.4.2](#)). If dose reduction to less than dose level -2 is required for neutropenia, discontinue treatment with fludarabine, cyclophosphamide, and rituximab. If fludarabine and cyclophosphamide are delayed for neutropenia, rituximab should also be delayed.

NOTE: Patients who require a dose reduction during a given cycle will remain at that dose for future cycles and will not be re-escalated to higher dose levels.

In patients whose baseline (i.e., prior to starting protocol therapy) ANC is <1000/ μ L, the FCR dose modifications, if required, would not be applied until Cycle 3.

5.4.4 Dose Modifications for Febrile Neutropenia

- **Arm A**

For febrile neutropenia, hold Ibrutinib until fever resolves and ANC \geq 1000/ μ L, then resume Ibrutinib at the previous dose. If Ibrutinib is delayed for febrile neutropenia, rituximab should also be delayed.

- **Arm B**

For febrile neutropenia, hold fludarabine and cyclophosphamide until fever resolves and ANC \geq 1000/ μ L, then resume both at one dose level lower than the previous dose (see table in Section 5.4.2). If dose reduction to less than dose level -2 is required for febrile neutropenia, discontinue treatment with fludarabine, cyclophosphamide, and rituximab. If fludarabine and cyclophosphamide are delayed for febrile neutropenia, rituximab should also be delayed.

NOTE: Patients who require a dose reduction during a given cycle will remain at that dose for future cycles and will not be re-escalated to higher dose levels

5.4.5 Dose Modifications for Thrombocytopenia

- **Arm A**

Grade 3 thrombocytopenia (platelets $<50 \times 10^9$ /L [ie, $< 50,000$ /mL]); or in subjects with baseline thrombocytopenia a platelet decrease of 50% to 74% from baseline that is associated with clinically significant bleeding follow the actions outlined in the table:

Occurrence	Action
1 st	Hold Ibrutinib until recovery to Grade \leq 1 or baseline; may restart at original dose level (420 mg daily)
2 nd	Hold Ibrutinib until recovery to Grade \leq 1 or baseline; restart at 1 dose level lower (280 mg daily)
3 rd	Hold Ibrutinib until recovery to Grade \leq 1 or baseline; restart at 1 dose level lower (140 mg daily)
4 th	Discontinue Ibrutinib

Ibrutinib may be held for a maximum of 28 consecutive days. Study medication should be discontinued permanently in the event of a toxicity lasting more than 28 days.

For grade 4 thrombocytopenia (platelets $< 25 \times 10^9$ /L [ie, $< 25,000$ /mL]); or in subjects with baseline thrombocytopenia a decrease of $> 75\%$ from baseline or $< 20 \times 10^9$ /L, whichever is higher (note Section 5.1.1.1 for those with a baseline platelet count less than 20×10^9 /L) follow the actions outlined in the table:

Occurrence	Action
1 st	Hold Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level (420 mg daily)
2 nd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (280 mg daily)
3 rd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (140 mg daily)
4 th	Discontinue Ibrutinib

Ibrutinib may be held for a maximum of 28 consecutive days. Study medication should be discontinued permanently in the event of a toxicity lasting more than 28 days.

Patients who require a dose reduction during a given cycle will remain at that dose for future cycles and will not be re-escalated to higher dose levels.

- **Arm B**

Platelets must be $\geq 100,000/\mu\text{L}$ or $> 80\%$ of baseline value (i.e., $> 80\%$ of the value before protocol therapy started) on day 1 of a cycle. For platelets $< 100,000/\mu\text{L}$ or $< 80\%$ of baseline, hold fludarabine and cyclophosphamide until platelets $\geq 100,000/\mu\text{L}$ or $> 80\%$ of baseline, then resume both at one dose level lower than the previous dose. If dose reduction to less than dose level -2 is required for thrombocytopenia, discontinue treatment with fludarabine, cyclophosphamide, and rituximab. If fludarabine is delayed for thrombocytopenia, rituximab should also be delayed. Note Section [5.1.3.1](#) for those with a baseline platelet count less than $20 \times 10^9/\text{L}$.

In patients whose baseline (i.e., prior to starting protocol therapy) platelet count $< 100,000/\mu\text{L}$, these dose modifications, if required, would not be applied until Cycle 3.

5.4.6 Autoimmune Hemolytic Anemia or Thrombocytopenic Purpura

Patients on Arm B developing autoimmune hemolytic anemia (AIHA) or autoimmune thrombocytopenia (AIT) during fludarabine therapy will be removed from protocol therapy, and treated with alternative agents at the discretion of the local physician. In this event, please consult with the ECOG Study Chair.

NOTE: Patients remain “on study” until an endpoint, either progression or death, is reached.

5.4.7 Non-Hematologic Toxicity (not including nausea, vomiting, diarrhea, drug-related chills and hair loss except where specified)

- If multiple adverse events are seen, administer dose based on the greatest reduction required by any single adverse event observed.
- Dose modifications are for adverse events attributed to study treatment. Dose modifications are not required for adverse events unrelated to study treatment.

- Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- Ibrutinib may be held for toxicity consideration for a maximum of 28 consecutive days. Study medication should be discontinued permanently in the event of a toxicity lasting more than 28 days. If Ibrutinib is interrupted for a reason other than toxicity (e.g. unrelated illness) it must be restarted within 42 days. If interrupted for more than 60 days, study medication should be discontinued permanently
- Patients who require a dose reduction during a given cycle will remain at that dose for future cycles and will not be re-escalated to higher dose levels.
- If cough, dyspnea, and other pulmonary symptoms occur, a chest x-ray and high-resolution chest CT scan should be obtained. Incentive spirometry studies (to include DLCO).should be considered. Consider Pneumocystis pneumonia or viral pneumonitis.
- **Arm A**
 - Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic or anti-diarrheal therapy) or any other Grade 4 toxicity or any unmanageable Grade 3 toxicity follow the actions outlined in the table:

Occurrence	Action
1 st	Hold Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level (420 mg daily)
2 nd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (280 mg daily)
3 rd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (140 mg daily)
4 th	Discontinue Ibrutinib

Patients who require a dose reduction during a given cycle will remain at that dose for future cycles and will not be re-escalated to higher dose levels.

- **Arm B**
 - For non-hematologic toxicity ≥ grade 2 attributable to fludarabine, reduce fludarabine by 50%.
 - For non-hematologic toxicity ≥ grade 2 attributable to cyclophosphamide, reduce cyclophosphamide by 50%.
 - If cough, dyspnea, and other pulmonary symptoms occur, a chest x-ray and high-resolution chest CT scan should be obtained. Incentive spirometry studies (to include DLCO).should be considered. Consider Pneumocystis pneumonia or viral pneumonitis.

5.4.8 Anti-coagulant therapy for patients on Arm A

Patients who require initiation of anticoagulant treatment (eg, heparin or warfarin) while on treatment with Ibrutinib should have Ibrutinib held until stable on anticoagulant therapy. Patients receiving Ibrutinib may not receive concomitant warfarin or other vitamin K antagonists and should receive alternative anti-coagulants. Once Ibrutinib is restarted, patients should be followed closely during the co-administration of Ibrutinib and anticoagulant therapy. No dose reduction is required when Ibrutinib is restarted.

5.5 Supportive Care

5.5.1 All patients must receive daily allopurinol (300 mg/day PO) for days 1-14 of cycle 1 of therapy on both treatment arms unless they are allergic. Patients on Arm A (Ibrutinib/Rituximab) will also receive allopurinol (300 mg/day PO) for days 1-14 of cycle 2 since that is the first cycle they receive rituximab. The need for allopurinol with subsequent induction cycles is left to the discretion of the treating physician. For patients with an allergy to allopurinol that precludes administration, patients can be followed closely for tumor lysis syndrome without allopurinol and the use of rasburicase as needed at the discretion of the treating physician.

5.5.2 Patients on both study arms will receive Bactrim DS 1 tablet (or alternative Pneumocystis pneumonia prophylaxis) on Monday/Wednesday/Friday AND acyclovir 400 mg p.o. twice per day (or equivalent) beginning with cycle 1 and continuing until the time of response evaluation (52 weeks after start of cycle 1; see Section [7.1](#)). Even if patients discontinue protocol treatment, they should remain on these prophylactic anti-biotics until this timepoint.

5.5.3 Neutrophil growth factors are permitted per American Society of Clinical Oncology (ASCO) guidelines (JCO 24:3187-3205). Use of colony stimulating factors (e.g., filgrastim, sargramostim, PEG-filgrastim) in this protocol is permitted during therapy as required for the treatment of febrile neutropenia. Colony stimulating factors may not be used to avoid dose reductions (e.g. to boost counts immediately before a starting a treatment cycle). The use of colony stimulating factors must be noted on flow sheets.

5.5.4 Any blood transfusions administered must be irradiated blood products to reduce risk of transfusion mediated graft versus host disease in CLL patients receiving potentially T-cell suppressive therapy.

5.5.5 All supportive measures consistent with optimal patient care will be given throughout the study.

5.5.6 As of 2012, the Center for Disease Control (CDC) recommends routine use of the 13-valent pneumococcal conjugate vaccine (PCV12; Prevnar 13) for all adults with CLL and other immunocompromising conditions. Per the CDC, this should be administered **in addition to** the standard 23-valent pneumococcal vaccine (PCV-23; Pneumovax 23) received by most adults. Since

most CLL patients have not yet received Pevnar 13, all study patients who have:

- i) not previously received the Pevnar 13 pneumococcal vaccine
- ii) are \geq 12 months from their last Pneumovax (or have never received a Pneumovax)
- iii) are willing to receive vaccination

should receive Pevnar 13 vaccination at the time of their 12 month response evaluation. Additional information on the CDC guidelines can be found at:

<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm>

5.6 Duration of Therapy

Patients will receive protocol therapy unless:

- 5.6.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E1912 Forms Completion Guidelines.
- 5.6.2 Patient withdraws consent.
- 5.6.3 Patient experiences unacceptable toxicity.
- 5.6.4 Non-protocol therapies are administered.

5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 10 years from the date of registration. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

Patients should be reevaluated for progression every 4 weeks (+/-10 days) during the first 6 months of the study by physical exam and CBC. Although formal response evaluation will not occur until the 12 month response evaluation (or off study evaluation), patients will be evaluated prior to cycles 1-6 and 3 months after the end of cycle 6 of therapy to identify individuals who have experienced disease progression.

Prior to the formal response evaluation, baseline on study measurements will be used to determine disease progression (e.g. NOT cycle by cycle comparisons). Once patients undergo formal response evaluation, the nadir value at either baseline or time of response will be used for evaluating future disease progression.

NOTE: With the exception of SLL patients without palpable lymph nodes (see Section [6.1.1.1](#)) Information from CT scans is not considered in the standard classification of response which is based on the results of CBC, physical exam, and bone marrow examination. Accordingly, data from CT scans will be collected to document response and or persistence of non-palpable nodes at the time of formal response evaluation but will not be used in the primary response categorization.

6.1 Assessment of Clinical Response

The major criteria for determination of the response to therapy in patients with CLL are based on physical examination and evaluation of peripheral blood and bone marrow. It is recommended that the laboratory and radiographic studies which are abnormal pre-study be repeated to document the degree of maximal response.

6.1.1 Complete remission requires all of the following for a period of at least 2 months (e.g. 2 occasions at least 4 weeks apart):

6.1.1.1 Absence of lymphadenopathy by physical examination and appropriate radiographic techniques (e.g. all lymph nodes \leq 1.5 cm). For patients whose only measurable disease at the time of enrollment is on CT scan (i.e. SLL with no palpable nodes), a CT scan is required before classifying the patient a CR.

6.1.1.2 Absence of hepatomegaly or splenomegaly by physical examination.

6.1.1.3 Absence of constitutional symptoms (fevers, nights sweats, weight loss, fatigue) due to disease.

6.1.1.4 Normal CBC as exhibited by:

6.1.1.4.1 Polymorphonuclear leukocytes \geq 1500/ μ l.

6.1.1.4.2 Platelets > 100,000/ μ l (untransfused).

6.1.1.4.3 Hemoglobin > 11.0 gm/dl (untransfused).

6.1.1.4.4 Peripheral blood lymphocytes \leq 4000/ μ l.

NOTE: Patients who fulfill all criteria for a CR but who have a persistent anemia, thrombocytopenia, or

neutropenia related to drug toxicity rather than residual CLL will be classified as CR with incomplete marrow recovery (CRi) according to the international criteria.

- 6.1.1.5 One marrow aspirate and biopsy should be performed 52 weeks after Day 1 of cycle 1 (see Section [7.1](#)) among patients with clinical and laboratory evidence of a CR to document that a complete remission has been achieved. The marrow sample must be at least normocellular with < 30% of nucleated cells being lymphocytes. If it is hypocellular, a repeat determination should be made in 2-4 weeks. Samples are to be analyzed by a pathologist and the presence or absence of nodules noted, although not included in the current definition of CR.

NOTE: In a subset of patients who are otherwise in a CR, bone marrow nodules can be identified histologically. In such cases, special stains will be performed to determine whether such nodules represent “regenerative nodules” or residual “clonal nodules”. The presence of regenerative nodules is consistent with CR while the presence of residual clonal nodules will be classified as a nPR (nodular PR) which is a sub-classification of PR.

- 6.1.1.6 Any other laboratory assays (e.g., quantitative immunoglobulins) will not be used currently as an index for response but will be recorded for clinical correlations.

6.1.2 To be considered in PR, the patient must exhibit the features in Sections [6.1.2.1](#), [6.1.2.2](#), and [6.1.2.3](#) (if abnormal prior to therapy) as well as one or more of the remaining features (Sections [6.1.2.4](#), [6.1.2.5](#), [6.1.2.6](#)) for at least 2 months (e.g. 2 occasions at least 4 weeks apart). In addition to the parameters listed below, the presence or absence of constitutional symptoms will be recorded.

- 6.1.2.1 $\geq 50\%$ decrease in peripheral blood lymphocyte count from the pretreatment baseline value.
- 6.1.2.2 $\geq 50\%$ reduction in lymphadenopathy. For patients whose only measurable disease at the time of enrollment is on CT scan (i.e. SLL with no palpable nodes), a CT scan demonstrating $\geq 50\%$ reduction of target nodes enlarged at baseline is required before classifying the patient a CR.
- 6.1.2.3 $\geq 50\%$ reduction in size of liver and/or spleen as measured by physical exam noting the maximal distance below the respective costal margins of the palpable hepatosplenomegaly during rest.

- 6.1.2.4 Polymorphonuclear leukocytes \geq 1500/ μ l or 50% improvement over baseline.
- 6.1.2.5 Platelets > 100,000/ μ l or 50% improvement over baseline.
- 6.1.2.6 Hemoglobin > 11.0 gm/dl or 50% improvement over baseline without transfusions.
- 6.1.3 Progressive disease (PD)
- Progressive Disease (PD) will be characterized by at least one of the following:
- 6.1.3.1 \geq 50% increase in the sum of the products of at least 2 lymph nodes on 2 consecutive examinations 2 weeks apart (at least 1 node must be \geq 2 cm) and not due to tumor flare reaction. Appearance of new palpable lymph nodes > 1.5 cm not due to tumor flare reaction.
- 6.1.3.2 \geq 50% increase in the size of liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly which was not previously present not due to tumor flare reaction.
- 6.1.3.3 \geq 50% increase in the absolute number of circulating lymphocytes (taking as a reference for progressive disease the smallest absolute lymphocyte count recorded since the treatment started) not due to tumor flare reaction. The absolute lymphocyte count must be at least 5×10^9 /L to qualify as disease progression.
- NOTE:** It is common for CLL patients to experience a transient increase in lymphocytosis due to redistribution of lymphocytes from the lymph nodes and spleen to the peripheral blood circulation. This lymphocytosis is NOT a marker of disease progression or Richter's transformation and typically resolves over several months. For this reason, prior to the 12 month response evaluation, patients on both arms will not be considered to have disease progression based on an increased absolute lymphocyte count if they simultaneously have unequivocal improvement in at least one other disease-related parameter including lymph node size, spleen size, hematologic parameters (Hgb or platelet count), or disease-related symptoms. Questions regarding an increase in the absolute lymphocyte count after initiation of therapy should be discussed with the study PI.
- 6.1.3.4 Unscheduled CT Scans: Since this is an open label trial, it is possible that an imbalance in unscheduled CT scans could emerge between arms and influence assessment of disease progression. To address this issue, all

unscheduled CT scans performed on both arms as well as the reason for unscheduled CT scans will be recorded. This information will be collected to identify differences in the frequency of such unscheduled CT scans between arms and allow us to detect potential bias in ascertainment of disease progression (see Section 9.3.1.2).

6.1.3.5 Progression by physical exam only: It is anticipated that most cases of disease progression will initially be identified by an objective increase in the absolute lymphocyte count (ALC) on a complete blood count or simultaneous increase in ALC and progressive lymphadenopathy.

Given the unblinded nature of the trial however, it is possible that a difference in the interpretation of palpable lymphadenopathy could occur between arms. As detailed in Section 6.1.3.5, to address this possibility, we will record the pattern of relapse by classifying all patients experiencing progression as:

- Progression due to rising ALC only
- Progression determined by lymphadenopathy on physical exam only
- Progression due to both rising ALC and physical
- Exam

This information will be evaluated to identify potential bias due to differences in the interpretation of palpable lymphadenopathy between arms (Section [9.3.3](#)).

6.1.3.6 In the absence of progression as defined above, the presence of a ≥ 2 gm/dl decrease in hemoglobin, or $\geq 50\%$ decrease in platelet count and/or absolute granulocyte count will not exclude a patient from continuing on study. Bone marrow aspirate and biopsy are strongly encouraged to better define the cause of the suppressed counts.

6.1.3.7 Transformation to a more aggressive histology (e.g. Richter's syndrome or prolymphocytic leukemia with $> 55\%$ prolymphocytes).

6.1.3.8 For patients who achieve a CR or nodular PR < progression will be defined as recurrence of circulating leukemia cell clone in the peripheral blood and an absolute lymphocyte count $> 5 \times 10^9/L$ and/or recurrence of palpable lymphadenopathy > 1.5 cm by physical exam.

6.1.4 Stable Disease (SD)

6.1.5 Patients who have not achieved a CR or a PR, or who have not exhibited findings consistent with Progressive Disease will be considered as having Stable Disease.

6.1.6 Complete Clinical Remission (CCR)

- 6.1.7 Patients who have clinical and laboratory evidence of CR but who have not yet had a bone marrow biopsy to distinguish between CR and nPR will be classified as having a complete clinical response (CCR) until the marrow biopsy is obtained.
- 6.1.8 Evaluation of Minimal Residual Disease (MRD): An important aspect of this trial is that evaluation of minimal residual disease using a sensitive flow cytometry method capable of detecting approximately 1 CLL cell per 10,000 leukocytes following induction.

An International, standardized approach for flow cytometric evaluation of residual disease in patients with CLL was recently developed (32). This approach reliably detects residual CLL B-cells at the level of 1 leukemic cell per 10,000 leucocytes. Notably, analysis of peripheral blood was equally or more sensitive to marrow in 92% of samples except when patients had received treatment with monoclonal antibodies (such as rituximab) within 3 months of evaluation.

This approach uses a pre-antibody ammonium chloride red cell lysis approach to separate peripheral blood white blood cells from RBCs followed by staining of $1-2 \times 10^6$ leukocytes with a panel of antibodies for flow cytometry analysis. For each test, 300,000 to 500,000 events were collected to ensure the desired sensitivity of the assay.

While the 4 color based strategy was the standard proposed by the international group, 5- to even 8-color flow cytometry based assays are being used in many laboratories and are expected to have a similar degree of sensitivity (level of 1 leukemic cell per 10,000 leucocytes) while enhancing the accuracy of the assay.

Assessments for MRD in the present study will be conducted as a research assay in the Mayo Clinic Rochester Department of Hematopathology under the direction of Dr. Curtis Hanson using a flow cytometry strategy able to detect residual leukemia at the level of 1 leukemic cell per 10,000 leukocytes in accord with the International Standard (32). For each test, 200,000 to 500,000 events are collected to ensure the desired sensitivity of the assay.

All patients will undergo assessment of MRD using sensitive flow cytometry 52 weeks (+/- 14 days) after day 1 of cycle 1 (see Section 7.1). Since the assessment of MRD 52 weeks after day 1 of cycle 1 will occur more than 3 months of rituximab therapy, MRD assays will be performed on peripheral blood. MRD testing for research purposes will be performed at other time-points as indicated in Section 7.

- 6.1.9 Quality of Life

CLL and CLL treatment can have a substantial affect on patient quality of life.

While Ibrutinib appears to have a favorable toxicity profile relative to fludarabine based therapy, the need for chronic indefinite administration may result in chronic side effects that ultimately erode QOL over the long run (compared to a more intense but limited duration treatment schedule). In addition, the benefit of lower toxicity

may not ultimately improve QOL if this treatment is less effective at controlling the disease.

To explore these aspects, the present study is designed to assess the QOL of patients on both treatment arms longitudinally. Mandatory quality of life will be assessed at the following 8 time-points:

- Baseline
- After 3 cycles of therapy
- After 6 cycles of therapy
- At response evaluation (52 weeks after day 1 of cycle 1)
- Every 6 months for 2 years after response evaluation
- At disease progression

The QOL of patients in the treatment arms will be compared at these time points to assess affect of treatment arm on QOL both during active the first several months of treatment and over the long term.

Primary Endpoint

Quality of life (QOL) will be assessed using FACT-G and the leukemia subscale. The primary objective of the QOL study is to compare treatment toxicity-related QOL in patients receiving the experimental Ibrutinib -based therapy to those receiving standard FCR. The primary interest is the FACT-Leu Trial Outcome Index (TOI), which is comprised of the FACT-G physical well-being (PWB) and functional well-being (FWB) subscales and the leukemia subscale. The FACT-Leu TOI contains a total of 31 items, with scores ranging from 0 to 124. It will be administered at the following time points: at the time of randomization, three months and six months after randomization, and every six months thereafter. The primary endpoint is the change in FACT-Leu TOI score from the time of randomization to 12 months after beginning therapy between the FCR arm and the Ibrutinib arm.

To better understand the impact of CLL on an individual's QOL, the entire FACT-G Leukemia questionnaire will be administered to all patients at the time of study enrollment, i.e., prior to initiating therapy. The FACT-G Leukemia is a 43-item instrument, containing the subscales previously described above. In addition, it also contains a social and an emotional well-being subscale.

Adherence:

In addition to longitudinally measuring QOL, we will also assess adherence to therapy in the Ibrutinib arm given that it is a chronic oral therapy. Adherence will be assessed using both the pill diary ([Appendix III](#)) completed with each cycle as well as the Morisky Adherence Scale.). The Morisky scale will be completed by patients on the Ibrutinib arm at treatment cycle 3, treatment cycle 6, month 12 (52 week) and month 24.

7. Study Parameters

7.1 Therapeutic Parameters

1. Prestudy scans or x-rays used to document measurable or evaluable disease must be done within 2 weeks of registration.
2. Prestudy CBC with differential, LFTs must be done \leq 2 weeks before registration.
3. All required prestudy chemistries must be done \leq 2 weeks before registration - unless specifically required on Day 1 as per protocol. If abnormal, they must be repeated within 48 hours prior to registration.

NOTE: All scheduled visits and testing +/- 4 days.

Tests/Procedures	Active Monitoring Phase						Follow Up
	Pre-treatment	During Treatment			12 Month Response Evaluation	Observation and/or Continuation	
	\leq 14 days prior to registration	Day 1 of Cycles 1-6	Prior cycle 7 (arm A) or End of Cycle 6 (arm B)	3 months after end cycle 6	52 weeks after Day 1 of cycle 1 (+/- 14 days)	Every 90 days (+/- 14 days)	
Tests & Observations							
History and progress note	X	X	X	X	X	X	
Performance status	X	X	X	X	X	X	
Height	X						
Weight/Body Surface Area ¹	X	X			X		
Physical examination	X	X	X	X	X	X	
Tumor measurement by physical exam	X ²	X ²	X ²	X ²	X ²	X ²	
Drug toxicity measurement	X	X	X	X	X	X	
Comorbidity Index	X ³						
Timed Up and Go (TUG) Test ¹³	X						
Laboratory Studies							
CBC with differential	X	X ⁴	X ⁴	X	X	X	
Serum creatinine, CrCl (estimate)	X	X ⁵					
Uric acid, glucose, phosphate, Ca ⁺⁺	X	X ⁵					
AST, ALT, total bilirubin, alkaline phosphatase	X	X	X	X	X	X	
Peripheral blood immunophenotyping by flow cytometry	X						
Serum pregnancy test	X ⁶						
CLL FISH panel (on peripheral blood or bone marrow aspirate)	X ⁷						
Bone marrow aspirate and biopsy	X ⁸				X ⁸		

Tests/Procedures	Active Monitoring Phase						
	Pre-treatment	During Treatment			12 Month Response Evaluation	Observation and/or Continuation	Follow Up
Beta-2-microglobulin	X				X		
Quantitative Immunoglobulins (IgG, IgA, IgM)	X				X		
Hepatitis B (HB) surface antigen, surface Ab and core Ab testing;	X ⁹						
Hepatitis C Ag testing	X ¹¹						
Direct Coombs test	X						
CT scan chest, abdomen, pelvis	X				X		
Biological Sample Submissions	See Section 7.2						
QOL Questionnaires ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰		X ¹⁰	X ¹⁰	

Footnotes for Test Schedule

1. Drug doses need not be changed unless the calculated dose changes by >10%
2. Physical exam should measure the spleen and liver noting the maximal distance below the respective costal margins at rest and should record the bidimensional diameter of the largest palpable node in each lymph node area of involvement including the following 6 sites: cervical (right and left) axillary (right and left), inguinal (right and left).
3. Cumulative illness rating scale – see [Appendix VII](#) (JCO 16: 1582–1587).
4. For cycle 1, patients with pretreatment platelet counts < 20x10⁹/L, should have a CBC repeated on Day 3. If this platelet count is below 20x10⁹/L, the responsible physician should be contacted and platelets should be transfused, if clinically indicated. As treatment with anti-CD20 monoclonal anti-bodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts < 50x10⁹/L prior to receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.
5. In Arm B obtain also prior to fludarabine dose on Day 2 of Cycle 1 to monitor for tumor lysis.
6. For women of childbearing potential only. Must be done ≤ 7 days prior to registration.
7. Must be done ≤ 3 months prior to registration.
8. Bone marrow biopsy is required. Baseline bone marrow biopsy requirement can be waived at the discretion of the study chair if the patient has had bone marrow biopsy obtained for clinical purposes ≤ 3 months prior to registration. At time of response evaluation a bone marrow biopsy is required for all patients with evidence of response (CR, PR) or stable disease but is not required for those with disease progression.
9. All patients must be screened for hepatitis B infection before starting treatment. Those patients who test positive for hepatitis B are ineligible.
10. Quality of life will be evaluated at baseline, after the first 3 cycles of therapy; after 6 cycles of therapy; at the time of the 12 month response evaluation, and then every 6 months for 2 years. QOL will also be assessed any time patient progresses.
11. If Hepatitis C antigen testing is positive, PCR to evaluate active Hepatitis C. Patients with active Hepatitis C are ineligible (see Section [3.1.17](#)).
12. Baseline CT scan requirement can be waived at the discretion of the study chair if the patient has had a CT scan ≤ 4 weeks prior to registration. At time of response evaluation CT scan is required for all patients with evidence of response (CR, PR) or stable disease but is not required for those with disease progression.
13. Please see [Appendix X](#) for instructions for the Timed Up and Go (TUG) Test.

7.2 Biological Sample Submissions

1. Bone marrow sections/slides must be submitted for central histological review at baseline and at the time of the twelve (12) month response evaluation as outlined in Section [10](#).
2. Peripheral blood and smears must be submitted at baseline for central review as outlined in Section [10](#).

NOTE: ECOG Institutions: Patients must be registered to E3903, Ancillary Laboratory Protocol for the Collection of Diagnostic Material on Patients Considered for ECOG Treatment Trials for Leukemia or Related Hematologic Disorders.

NOTE: E3903 is currently not open at the CTSU. Therefore, Intergroup/CTSU institutions are exempt from participating in E3903.

3. Peripheral blood should be submitted at baseline for banking, per patient consent.
4. Peripheral blood and buccal cells (baseline only) should be submitted at multiple time points as outlined below for correlative studies, per patient consent.

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG Coordinating Center regarding logistics for submission of fresh samples.

NOTE: An informed consent MUST be signed prior to the submission of any samples for any laboratory study and/or banking. Samples for the optional laboratory studies and/or banking should be submitted only from patients who have given written consent for the use of their samples for these purposes.

NOTE: It is required that biological sample submissions be logged into the ECOG Sample Tracking System (STS) (see Section [10.4](#)) for purposes of monitoring compliance and determination of reimbursement levels.

Biological Materials	Baseline ¹	After Three (3) Cycles of Therapy	After Six (6) Cycles of Therapy [Prior to Cycle Seven (7) Arm A, End of Cycle Six (6) Arm B]	Twelve (12) Month Response Evaluation (52 weeks after day 1 of cycle 1)	18, 24, and 36 months after randomization	Time of Disease Progression or Relapse	Ship To:
MANDATORY for Central Review							
Bone Marrow Sections/Slides	X			X			LTSL ²
Bone Marrow/Peripheral Blood Smears (Wright-Giemsa stained) ⁴	X						LTSL
Peripheral Blood (heparin, (4) 10mL green or purple [EDTA] top tubes, 30-40mL) ⁴	X						LTSL
From Patients Who Answer "YES" to "I agree to participate in the laboratory research studies that are being done as part of this clinical trial."							
Peripheral Blood (sodium heparin (5) 10mL green top tubes)	X	X	X	X	X	X	Mayo Clinic ³
Peripheral Blood (serum, (2) 10mL red top tubes)	X			X			Mayo Clinic ³
Buccal Swab or Rinse ⁴	X						LTSL
From Patients Who Answer "YES" to "I agree to provide additional blood for research."							
Peripheral Blood (serum, (2) 10mL red top tubes, 15-20mL) ⁴	X						LTSL

1. After randomization, prior to treatment.
2. Submit to the ECOG Leukemia Translational Studies Laboratory (LTSL). Signed E3903 patient consents and HIPAA authorizations must be submitted to the LTSL prior to or at time of submission of baseline samples per Dr. Paietta's institutional regulations. If E3903 is not open at ECOG institution or for Intergroup/CTSU institutions, the signed E1912 consent must be submitted.
3. Collection and shipping kits are being provided for the peripheral blood being submitted to Mayo Clinic.
4. If submitted as part of E3903 no additional samples are required on E1912.

8. Drug Formulation and Procurement

Drug Ordering: *Pharmacyclics* is supplying Ibrutinib (PCI-32765), through the Division of Cancer Treatment and Diagnosis, NCI, for this protocol. Maintenance of NCI drug accountability records is required. Ibrutinib (NSC 748645 IND 117241) may be requested by the Principal Investigator (or their authorized designees) at each participating institution.

The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (<https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx>). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (<https://eapps-ctep.nci.nih.gov/iam/>) and the maintenance of an “active” account status and a “current” password.

Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (<http://ctep.cancer.gov>) or by calling the PMB at (240) 276-6575.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (<http://ctep.cancer.gov>) or by calling the PMB at (240) 276-6575.”

8.1 Ibrutinib (NSC 748645) PCI-32765

8.1.1 Chemical name: 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one

8.1.2 Classification Selective, irreversible, small molecule inhibitor of Bruton’s tyrosine kinase (BTK).

8.1.3 CAS Registry Number: 936563-96-1 M.W.: 440.5 g/mole

8.1.4 Mode of Action

Ibrutinib binds covalently to a cysteine residue in the BTK active site, leading to potent and irreversible inhibition of BTK enzymatic activity of B-cell receptors (BCR). B-cell maturation is mediated by BCR

- signal transduction and BTK is an essential part of the signaling pathway.
- 8.1.5 Description
White to off-white crystalline solid
- 8.1.6 Storage and Stability
Ibrutinib Hard Gelatin Capsules should be stored at 15 – 25°C. Shelf life surveillance of the intact bottles is ongoing.
- 8.1.7 Administration
Orally, with 8 ounces (approximately 240 ml) of water. The capsules are to be swallowed intact, not less than 30 minutes before or 2 hours after a meal. Patients should avoid consuming food and beverages containing grapefruit juice or Seville oranges for the duration of the study due to CYP3A4/5 inhibition. Doses are to be taken at about the same time each day. If an ibrutinib dose is missed, it should be made up as soon as possible on the same day with a return to the normal schedule the following day.
- 8.1.8 Preparation
Ibrutinib is supplied as hard gelatin capsules containing micronized Ibrutinib and the following excipients: microcrystalline cellulose; croscarmellose sodium; sodium lauryl sulfate; may contain magnesium stearate.
- 8.1.9 Availability / How supplied
Ibrutinib is supplied by Pharmacyclics, Inc., and distributed by the CTEP, DCTD, NCI. Capsules are packaged in 60-ml high-density polyethylene (HDPE) bottles with an induction seal and a child resistant screw top cap. Each bottle contains 92 capsules.
- 8.1.10 Dose Specifics
Arm A 420 mg PO, each day, days 1-28. Capsules are 140mg strength in a size 0, gray, hard gelatin capsule.
- 8.1.11 Side Effects
See CAEPR, Section [Error! Reference source not found.](#)
- 8.1.12 Potential Interactions
Ibrutinib is metabolized primarily by CYP3A4/5. Due to this potential increase in Ibrutinib exposure, concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A4/5 can increase ibrutinib exposure and should be avoided (see [Appendix VIII](#)). Patients should also be advised to avoid vitamin E and fish oils. Strong inducers of CYP3A4/5 should be avoided. A comprehensive list of inhibitors, inducers, and substrates may be found at <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>. This website is continually revised and should be checked frequently for updates. Alternative agents with mild or no CYP3A4/5 inhibition should be considered. Co-administration of ketoconazole, a strong CYP3A4/5 inhibitor, in 18 healthy subjects, increased dose normalized exposure

(C_{max} and AUC_{0-last}) of ibrutinib by 29- and 24-fold, respectively. Therefore, concomitant administration of ibrutinib with strong inhibitors of CYP3A4/5 (see [Appendix VIII](#)) should be avoided.

If a strong CYP3A4/5 inhibitor must be used, the Medical Monitor should be consulted before the use, and a dose reduction of ibrutinib to 140 mg daily or temporary hold of ibrutinib should be considered. Subjects should be closely monitored for potential treatment-related toxicities. If ibrutinib is temporarily held or the dose reduced due to administration of strong CYP3A4/5 inhibitors, patients may return to the previous dose of ibrutinib once they are no longer taking strong CYP3A4/5 inhibitors. Moderate CYP3A4/5 inhibitors (see [Appendix VIII](#)) should be used with caution. If the benefit outweighs the risk and a moderate CYP3A4/5 inhibitor must be used, monitor subject for toxicity and follow dose modification guidance in the individual protocols, as needed (or consult the Medical Monitor). Grapefruit juices and Seville oranges may also increase ibrutinib plasma concentrations and should be avoided for the duration of ibrutinib treatment.

Warfarin and other vitamin K antagonists are not permitted in combination with ibrutinib. Patients should also be advised to avoid fish oil and vitamin E supplements while taking ibrutinib.

Although short term use (< 4 weeks) of pulse steroids are permitted, long term use of prednisone at a dose > 20 mg per day (or equivalent) is not permitted.

8.2 Allopurinol (Lopurin, Zyloprim)

8.2.1 Availability

Commercially available as 100 mg and 300 mg tablets. Please refer to the agent's package insert for additional information.

8.2.2 Preparation

A 20 mg/mL suspension may be made by crushing eight 300 mg tablets and mixing with 120 mL of either 1:1 mixture of Ora-Sweet® and Ora-Plus® or a 1:1 mixture of Ora-Sweet®SF and Ora-Plus®. The resulting suspension is stable for 60 days refrigerated.

8.2.3 Storage & Stability

Store tablets in a tight container at 15°-30°C.

8.2.4 Administration

300 mg/day by mouth days 1 through 14 (total of 14 days) of cycles 1 and 2 unless allergic. See Section [5.1.1.3](#).

Administer by mouth. Fluid intake should be sufficient to yield a daily urine output of 2 liters.

8.2.5 Toxicity

Dermatologic toxicity, including pruritic maculopapular rash, urticaria, exfoliative dermatitis, and hemorrhagic dermatides which may be accompanied by alopecia, fever, and malaise. Stevens-Johnson

syndrome (exfoliative dermatitis with mucous membrane involvement) has been reported. Patients with compromised renal function may be at a greater risk of development of rashes. Skin reactions may be delayed as long as two years after initiation of therapy.

Gastrointestinal side effects, including nausea, diarrhea, and abdominal pain may occur. Drowsiness may also occur.

8.2.6 Drug Interactions

Concomitant usage of allopurinol and drugs that can increase serum urate concentrations, e.g., diuretics and alcohol, may necessitate an increase in allopurinol dosage. Administration of allopurinol with ampicillin or amoxicillin may increase the risk of skin rash. Allopurinol and chlorpropamide may result in an increased risk of hypoglycemia, whereas allopurinol with co-trimoxazole is associated with increased risk of thrombocytopenia.

8.3 Rituximab (IDEC-C2B8, Rituxan®)

8.3.1 Availability

Rituximab is commercially available in 10 mL and 50 mL single-use vials containing 100 mg or 500 mg rituximab solution, respectively, at a concentration of 10 mg/mL. Please refer to the agent's package insert for additional information.

8.3.2 Storage & Stability

Intact vials should be stored under refrigeration (2°-8°C). Dilute solutions for infusion (1-4 mg/mL) are stable for 24 hours under refrigeration, and for an additional 24 hours at room temperature.

8.3.3 Preparation

The desired dose of rituximab should be diluted in 0.9% NaCl or D₅W to a final concentration of 1-4 mg/mL. The solution should be mixed by gently inverting the bag.

8.3.4 Administration

Arm A:

Cycles 2 through 7

Rituximab, 50 mg/m² IV on day 1 of Cycle 2, and 325 mg/m² on day 2 of Cycle 2,

then 500 mg/m² on day 1 of Cycles 3-7.

Arm B

Cycles 1 through 6

Rituximab, 50 mg/m² IV on day 1 and 325 mg/m² on day 2 of Cycle 1 and 500 mg/m² on day 1 of Cycles 2-6.

8.3.5 Side Effects

Refer to package insert for rituximab for additional information.

Likely side effects include: Chills, Fever, Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing, Lowered white blood cell count, Less likely side effects include: Lowered red blood cell count (may cause anemia, weakness, fatigue) Fever associated with dangerously low levels of a type of white blood cell (neutrophils), Heart attack caused by a blockage of a blood vessel supplying part of the heart, Fast heartbeat, Belly pain, Diarrhea, Nausea or the urge to vomit, Vomiting, Swelling of the arms and/or legs, Fatigue or tiredness, Pain, Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing. Allergic reaction to other medications, injected proteins, or antisera (blood product) used to treat certain medical conditions (such as an infectious or poisonous substance), Infection, Awakening of viruses which have been latent/dormant, Infection in HIV positive patients, Lowered platelet count that might interfere with clotting (may make you more likely to bruise or bleed), Decrease in the total number of white blood cells (leukocytes), Increased blood sugar level, Decreased blood level of calcium, Decreased blood level of potassium, Joint pain, Back pain, Muscle pain, Pain in the area of the tumor, Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness), Headache or head pain, Abnormal drowsiness or sluggishness, an unusual lack of energy, Convulsion or seizure, Sudden or traumatic injury to the kidney, Stuffy or runny nose, sneezing, Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath, Cough, Shortness of breath, Decrease in the oxygen supply to a tissue, Inflammation of the lungs that may cause difficulty breathing and can be life-threatening, Sore throat, Excess sweating, Itching, Skin rash, Swelling of body tissue underneath the skin, Hives, Sudden reddening of the face and/or neck, High blood pressure, Low blood pressure. Rare but serious side effects include: Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness. Group of signs and symptoms due to rapid breakdown of tumor that can occur after treatment of cancer has started that causes increased levels of blood potassium, uric acid, and phosphate, decreased levels of blood calcium, and kidney failure. Disease affecting brain tissue, caused by the JC virus. Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs. Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue. Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer). Life-threatening condition affecting greater than 30% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)

8.4 Fludarabine Monophosphate [Fludara; Berlex laboratories]

8.4.1 Availability

IV: Fludarabine monophosphate is commercially available as a sterile powder in 50 mg vials containing 50 mg of mannitol and sodium hydroxide to adjust the pH to 7.7. Please refer to the agent's package insert for additional information.

PO: An oral formulation of fludarabine will be used by Canadian institutions. Fludarabine is available in 10 mg tablets.

8.4.2 Storage & Stability

Intact vials should be stored under refrigeration (2°-8°C). Reconstituted fludarabine phosphate contains no antimicrobial preservative and thus should be used within 24 hours of reconstitution. Solutions diluted in D₅W or NS are stable for 48 hours at room temperature or under refrigeration.

8.4.3 Preparation

IV: Vials of fludarabine are reconstituted with 2 mL of sterile water for injection to yield a 25 mg/mL solution. The product should be further diluted for intravenous administration in 100 or 125 mL 5% dextrose or in 0.9% saline.

8.4.4 Administration

Fludarabine 25 mg/m² IV days 1, 2, 3

IV: Fludarabine will be administered as an IV infusion over 30 minutes.

8.4.5 Toxicity

Myelosuppression (dose limiting toxicity), fever, nausea and/or vomiting, skin rashes, myalgia, fatigue, autoimmune hemolytic anemia (may be life-threatening), and pulmonary toxicity (both pneumonia and pulmonary hypersensitivity reactions have been reported; fatal pulmonary toxicity has been described, especially when fludarabine was used in combination with pentostatin). Severe or fatal CNS toxicity presenting with loss of vision and progressive deterioration of mental status has been described primarily after high doses of fludarabine monophosphate, or at usual doses (25-30 mg/m²) in elderly patients. Very rarely described complications include transfusion-associated graft versus host disease, thrombotic thrombocytopenic purpura, and liver failure. Tumor lysis syndrome has been observed, especially in patients with advanced bulky disease. Opportunistic infections (protozoan, viral, fungal, and bacterial) have been observed. Please refer to the package insert for additional information. Please also see Section [8.5.6](#) for a list of possible side effects when used in combination with cyclophosphamide.

8.4.6 Drug Interactions

Chronic use of corticosteroids with fludarabine should be avoided due to a significant increase in opportunistic infections.

8.5 Cyclophosphamide (Cytoxan[®]; CTX; CPA; Endoxan[®]; Neosar[®]; Cytoxan Lyophilized[®])

8.5.1 Availability

Commercially available as a powder for injection in 100 mg, 200 mg, 500 mg, and 1 gram and 2 gram vials. Please refer to the agent's package insert for additional information.

8.5.2 Storage & Stability

Intact vials should be stored at room temperature. Reconstituted and diluted solutions are stable for 24 hours at room temperature and 6 days if refrigerated.

8.5.3 Preparation

Reconstitute 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials with 5, 10, 25, 50, or 100 mL of sterile water for injection or normal saline to give a final concentration of 20 mg/mL. Vigorous shaking and/or gentle warming may be necessary for non-lyophilized preparations. Bacteriostatic water for injection (paraben preserved only) may be used; benzyl alcohol derivatives may NOT be used. Further dilute in D₅W or normal saline for IV infusion.

8.5.4 Administration

Cyclophosphamide 250 mg/m² IV, days 1, 2, 3

Administer by slow IV push or IV infusion over 30 minutes.

All patients should be adequately hydrated before and several days after each cycle of treatment. This is especially important to minimize hemorrhagic cystitis as well as the occurrence of tumor lysis syndrome in patients with bulky adenopathy or leukocytes > 50,000/μL.

8.5.5 Toxicity

Myelosuppression, hemorrhagic cystitis, syndrome of inappropriate antidiuretic hormone (SIADH), fatigue, hyperuricemia, azospermia, amenorrhea, cardiotoxicity (myocardial necrosis) with high doses.

8.5.6 Possible side effects, Fludarabine combined with Cyclophosphamide

Some of the Risks and Side Effects with Fludarabine and Cyclophosphamide are listed below (additional information can be found in the package insert):

Likely: Lowered white blood cell count (neutrophils/granulocytes) that may lead to infection, Lowered platelets which may lead to an increase in bruising or bleeding, Lowered red blood cells which may cause anemia, tiredness, or shortness of breath, Lowered number of another type of white blood cells (lymphocytes) that may lead to infection, Fatigue, Nausea, Vomiting, Time away from work, Hair loss,

“Shingles.” If you develop a condition known as shingles (Herpes zoster infection of the skin), a skin rash caused by the chicken pox virus, it will be important that you notify your physician immediately. There is a medication available to treat shingles effectively, but only if the medication is started within 24-48 hours after the rash has developed. Should these side effects occur, they can be treated with blood products (transfusions), antibiotics, and a reduction in the amount of chemotherapy given to you. Until your immune system has recovered from treatment, any blood products you may receive should be irradiated. Less Likely: Allergic reaction, Severe allergic reaction that causes fever, aches and pains in the joints, skin rash, and swollen lymph glands, Stuffy or runny nose, sneezing, Sore throat, Abnormal fast heartbeat, Excessive sweating, Flushing, Itching, Rash, Swelling of the lips, eyes, tongue, and throat which can be severe, Hives, Diarrhea, High blood sugar, Low blood potassium, Dizziness, Convulsion or seizure, Abdominal pain, Pain such as back, joint, and/or muscle pain, Headache, Wheezing, Cough, Shortness of breath, Inflammation of the lung which may cause difficulty breathing and difficulty getting oxygen, Infertility or sterility, Irregular menstrual periods. Some women may not resume their periods, Abnormal production of a hormone that regulates salt and fluid excretion, Increased production of tears associated with the administration of cyclophosphamide, Metallic taste, Bladder irritation which may cause blood to appear in your urine. To minimize this side effect, patients are encouraged to drink fluids to promote frequent urination on the days of cyclophosphamide administration and one day afterwards. Rare But Serious: Destruction of red blood cells that may lead to anemia. Should this occur, it can be treated with blood transfusions, Changes in vision or changes in degree of alertness both of which can be severe or fatal, Rash which may become severe, Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the outer skin layer to separate from the middle layer, Life-threatening condition affecting greater than 30% of the skin in which cell death causes the outer layer of skin to separate from the middle layer, Severe lung dysfunction resulting in the inability to breathe which can be life-threatening, Allergic reactions to blood transfusions, Tumor lysis syndrome - a rapid decline in the number of tumor cells that can lead to kidney failure and/or chemical imbalances that may have a serious effect on other organs like your heart. If this were to occur, you would receive close monitoring and blood tests, as well as appropriate medical treatment, Liver problems/liver failure

9. Statistical Considerations

9.1 Study Design and Objectives

This is a randomized phase III study designed to evaluate the ability of Ibrutinib-based induction therapy to improve the efficacy and tolerability of fludarabine-based chemoimmunotherapy for patients ≤ 70 years old with untreated symptomatic CLL. Five hundred and nineteen (519) patients will be randomized 2:1 to the Ibrutinib arm (A, 346 patients) and the FCR control arm (B, 173 patients).

The primary objective is to definitively evaluate whether patients who receive Ibrutinib-Rituximab have significantly longer PFS than those receiving FCR. With the planned sample size, we will have 80% power to detect a true hazard ratio of 1.5 (FCR vs. Ibrutinib) while controlling the one-sided type I error at 2.5%. Overall survival will be used as a secondary endpoint. If PFS is found to be significantly longer in the Ibrutinib-Rituximab arm than the FCR arm, with an additional 34 months of follow-up, we will have 80% power to detect a true hazard ratio of 1.67 (FCR vs Ibrutinib) in terms of OS while controlling the one-sided type I error at 2.5%.

Interim analyses will be performed. The study will be monitored for early stopping in favor of superior PFS in the experimental Ibrutinib arm, or for evidence of lack of benefit.

Because of the expected lower toxicity and non-curative nature of the Ibrutinib therapy, quality of life (QOL) is an important secondary study objective for this study. Questionnaires will be administered to learn the QOL impact of disease as well as treatment in this patient population. If both PFS and OS are found to be significantly longer in the Ibrutinib arm than in the FCR arm, QOL results will be considered for labeling in the EU.

Summaries of other secondary objectives of the study are listed below. Details can be found in the Objectives section of the protocol.

- Evaluate patient overall survival (OS);
- Monitor and assess toxicity;
- Determine the effect of pre-treatment characteristics on outcome;
- Determine if the minimal residual disease (MRD) status is an effective marker for prolonged PFS and OS;
- Explore changes in genetic abnormalities and intra-clonal architecture pre and post treatment and their relationship with treatment resistance.
- Explore the effects of therapy on immune function (T-cell function, response to vaccinations)
- Validate SNPs found to be associated with efficacy and toxicity of fludarabine-based therapy in the E2997 trial;
- Develop and evaluate a prognostic model to predict clinical outcome;
- Evaluate signaling networks downstream of the B-cell receptor in patients receiving Ibrutinib-based therapy.
- Study mechanisms of resistance to FCR and Ibrutinib-based therapy.

9.2 Accrual

Based on previous studies conducted through the North American Intergroup collaboration (e.g. CALGB10404) in similar patient populations, we expect the annual accrual rate to be approximately 180 patients per year. It will take approximately 35 months to accrue the 519 patients for the study. Assuming median PFS for the Ibrutinib and FCR arms to be 78 and 52 months, respectively, the Ibrutinib vs. FCR comparison requires approximately 32 months of follow-up to reach full information of 203 events.

9.3 Primary Endpoint and Sample Size

The primary goal is to definitively evaluate whether patients who receive Ibrutinib-Rituximab have significantly longer progression-free survival (PFS) than those who do not. PFS is defined as the time from randomization to progression or to death without documentation of progression. We wish to have good power to detect a true hazard ratio of 1.5 (FCR vs. Ibrutinib regimen) controlling the one-sided type I error at 2.5%. Assuming PFS follows an exponential distribution, adjusted for sequential monitoring described below, a sample size of 519 patients randomized 2:1 to arms A (Ibrutinib) and B (FCR) with 346 and 173 patients in the two arms, respectively will yield a nominal 80% power to detect a hazard ratio of 1.5 (median PFS of 52 vs. 78 months in FCR vs. Ibrutinib) using a nominal one-sided $\alpha=0.025$ logrank test for the Ibrutinib-based regimen vs. FCR comparison. The required number of events for full information is 203.

A stratified logrank test applied to all patients as randomized will be the primary analysis, with age (< 60 years vs. \geq 60 years), ECOG performance status (0/1 vs. 2), disease stage (3/4 vs. 1/2), and baseline cytogenetic abnormalities (deletion of 11q23 vs. others) as stratification factors. The same analysis applied to eligible patients only will also be performed as a sensitivity analysis. Cox proportional hazards models will be used to assess possible effects of clinical and biological characteristics on outcome, including age, gender, disease stage, cytogenetic abnormalities, ECOG performance status, and important mutations. Treatment and covariate interactions will also be examined.

- 9.3.1 Since this is an unblinded trial, it is possible a difference in unscheduled CT scans could emerge between arms. All unscheduled CT scans performed on both arms as well as the reason for unscheduled CT scans will be recorded to identify differences in the frequency of unscheduled CT scans between arms (See Section [6.1.3.4](#)).
- 9.3.2 It is anticipated that most cases of disease progression will initially be identified by an objective increase in the absolute lymphocyte count (ALC) on CBC or simultaneous increase in ALC and progressive lymphadenopathy.
- 9.3.3 Given the unblinded nature of the trial however, it is possible that a difference in the interpretation of palpable lymphadenopathy could occur between arms. As detailed in Section [6.1.3.5](#), to address this possibility, we will record the pattern of relapse by classifying all patients experiencing progression as:
- Progression due to rising ALC only

- Progression determined by lymphadenopathy on physical exam only
- Progression due to both rising ALC and physical exam

These data will be used to evaluate the progression events on each arm of the study to assess whether there is a higher rate of progression by “physical exam only” in one study arm. Since we anticipate follow-up will be fairly mature before a large number of progression events occur on each arm, we will monitor differences in the pattern of progression at 6 month intervals from the outset of the trial and take action if the difference becomes larger than the greater of 10 patients or 20%. If this occurs, the research team will assess whether there needs to be changes to the criteria for progression for those patients in who progression is based solely on physical exam.

Collectively, these data will allow us to determine if there is an imbalance in progression based only on the findings of physical exam or a difference in the frequency of unscheduled CT scans and to detect potential bias in classification of disease progression on this basis.

9.4 Phase III Interim Analysis of the Primary Endpoint

We will perform the first interim analysis when follow-up is available through the later of 5 years after the start of accrual or 2 years after accrual is completed. The rationale is that if accrual takes 3 years to complete, then median follow-up should be at least 3.5 years at the time of the first efficacy analysis, while if accrual is faster or slower, the combination of the two rules would guarantee at least this much follow-up. If the study has reached the planned full information by this time, then the first analysis would be the only analysis. If the study is not at full information, then interim analyses will be performed annually until full information is reached. Under the assumed accrual rate and hazard rates for the two arms, interim and final analyses are expected to occur at 60 and 66 months after study activation. To preserve the overall type I error rate, critical values at the interim efficacy analyses will be determined using a truncated version of the Lan-DeMets error spending rate function corresponding to the O’Brien-Fleming (O-F) boundary. The upper O-F boundaries at the planned analyses times are shown in Table 1. If the upper O-F boundary is crossed at the interim analysis, that would be sufficient evidence of efficacy to stop the study in favor of the alternative.

Table 1: The Interim PFS Efficacy Analyses for Ibrutinib-Rituximab vs. FCR

Time from Study Start (Months)	Information Time	Events Under H_1	Truncated O-F Boundary
60	0.90	183	2.10
66.2	1.00	203	2.05

The study will also be monitored for early stopping for harm and inefficacy. At 25% information, the DSMC may consider stopping the study for harm if the lower 95% confidence bound for the hazard ratio (Ibrutinib/FCR) is above 1. Inefficacy monitoring is scheduled to start after approximately 49% of the full information becomes available with repeated analyses at each semi-annual DSMC meeting. Linear 20% Inefficacy Boundary (LIB20) proposed by Freidlin et

al. (2010) will be used [8]. At each interim analysis, if the estimated hazard ratio is larger than the cut-off value given in the LIB20 boundary, the study would be stopped early for lack of efficacy. In this study, the LIB20 boundary goes from 1 to 0.92 on the hazard ratio scale (from 0 to -0.08 on the log hazard ratio scale).

9.5 Secondary Objectives

Overall survival, defined as the time from randomization until death due to any cause, will be used as a secondary endpoint. Previous data showed that the time to 25% of FCR patients dying was 62.5 months [2]. Assuming an exponential survival distribution, with a total of 519 patients and adjusted for sequential monitoring described below, we will have 80% power to detect a true hazard ratio of 1.67 (FCR vs. Ibrutinib regimen) using a nominal one-sided $\alpha=0.025$ log-rank test. The required number of deaths for full information is 125. A hierarchical testing strategy will be used, in that the difference in OS between the two arms will be tested only if PFS for the Ibrutinib arm is significantly longer than that of the FCR arm, which gives us a one-sided family wise type I error rate of 2.5%.

We will perform the first interim analysis for OS at the final analysis time for PFS, expected at 66 months after study activation. To preserve the overall type I error rate, critical values at the interim efficacy analyses will be determined using a truncated version of the Lan-DeMets error spending rate function corresponding to the O'Brien-Fleming (O-F) boundary. The upper O-F boundaries at the planned analyses times are shown in Table 2. If the upper O-F boundary is crossed at an interim analysis, that would be sufficient evidence of efficacy in favor of the alternative.

Table 2: The Interim OS Efficacy Analyses for Ibrutinib-Rituximab vs. FCR

Time from Study Start (Months)	Information Time	Events Under H_1	Truncated O-F Boundary
66.2	0.63	78	2.60
83	0.82	102	2.27
100	1.00	125	2.04

A stratified logrank test applied to all patients as randomized will be the primary analysis for OS, with age (< 60 years vs. \geq 60 years), ECOG performance status (0/1 vs. 2), disease stage (3/4 vs. 1/2), and baseline cytogenetic abnormalities (deletion of 11q23 vs. others) as stratification factors. The same analysis applied to eligible patients only will also be performed as a sensitivity analysis. Cox proportional hazards models will be used to assess possible effects of clinical and biological characteristics on outcome, including age, gender, disease stage, cytogenetic abnormalities, ECOG performance status, and important mutations. Treatment and covariate interactions will also be examined.

As per NCI CTCAE Version 4.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either "unrelated or unlikely to be related" to study treatment in the event of an actual relationship developing.

9.6 Quality of LifePrimary Endpoint

Quality of life (QOL) will be assessed using FACT-G and the leukemia subscale. The primary objective of the QOL study is to compare treatment toxicity-related QOL in patients receiving the experimental Ibrutinib-based therapy to those receiving standard FCR. The primary interest is the FACT-Leu Trial Outcome Index (TOI), which is comprised of the physical well-being (PWB) and functional well-being (FWB) components of the FACT-G and the leukemia subscale. The FACT-Leu TOI contains a total of 31 items, with scores ranging from 0 to 124. The 31-item FACT-Leu instrument will be administered at the following time points: at the time of randomization, three months and six months after randomization, at the 12 month response evaluation, and every six months thereafter for two years. The primary endpoint is the change in FACT-Leu TOI score from the time of randomization to 12 months after beginning therapy between the FCR arm and the Ibrutinib arm. An analysis of the cases with both baseline and month 12 evaluations by randomized treatment group will be performed as the primary analysis. If both PFS and OS are found to be significantly longer in the Ibrutinib arm than in the FCR arm, results from this analysis will be considered for labeling in the EU.

The FACT-Leu TOI is reported to have a standard deviation (SD) ranging from 18.1 to 21.7. Assuming 90% 1-year survival, correlation of 0.4 or 0.6 between FACT-Leu TOI scores at randomization and 1 year after beginning therapy, and compliance rates (proportion of patients alive at one year who complete the baseline and 1-year QOL assessments) of 50%, 65% and 80%, the difference in FACT-Leu TOI mean change score between the Ibrutinib arm and the FCR arm we can detect with 80% power at two-sided significance level of 0.05 ranges from 4.9 to 9.4, and are shown in Table 3.

Table 3. Differences in FACT-Leu TOI mean change scores

Standard deviation (SD)	Correlation	SD of change	Difference detected 50% compliance n ₁ =156, n ₂ =78	Difference detected 65% compliance n ₁ =202, n ₂ =101	Difference detected 80% compliance n ₁ =250, n ₂ =125
18.0	0.4	19.7	7.7	6.7	6.0
18.0	0.6	16.1	6.3	5.5	4.9
20.0	0.4	21.9	8.5	7.5	6.7
20.0	0.6	17.9	7.0	6.1	5.5
22.0	0.4	24.1	9.4	8.2	7.4
22.0	0.6	19.7	7.7	6.7	6.0

Secondary Endpoints

The change in FACT-Leu TOI score from the time of randomization to 3 months after beginning therapy will be compared between arm A and arm B to assess the short-term effect of the two therapies on QOL.

The change in FACT-Leu TOI score from the time of randomization to 6 months after beginning therapy will be compared between the two treatment arms in order to provide additional information regarding the toxicity of the different regimens.

Repeated measures analysis techniques, which use data from all time points will be utilized to examine the treatment effect and time effect on FACT-Leu TOI score. Methods described in Schluchter [3] and Schluchter, Greene and Beck [4] will be used, which account for the possibility of informative missingness by jointly modeling the longitudinal QOL score and the time to dropout.

In addition, the social well-being and emotional well-being components of the FACT-G will be administered at study entry. The entire FACT-Leukemia instrument (FACT-G and the leukemia subscale) at baseline will be analyzed using descriptive statistics to assess the impact of CLL on QOL independent of treatment.

The Morisky Adherence Scale will be used to measure the likelihood that a patient will take prescribed medications for patients on the Ibrutinib arm, at 3, 6, 12 and 24 months after beginning therapy. Descriptive statistics will be used to summarize trend in adherence to prescription.

9.7 Correlative Studies

We will determine the effect of pre-treatment clinical and biological characteristics on clinical outcomes in terms of CR rates and PFS. Baseline characteristics of interest include disease stage and IGHV mutation status. We will also genotype a number of SNPs investigated in a previous ECOG trial E2997, which explored the association of these SNPs with the efficacy and toxicity of fludarabine-based therapy.

CR rates will be estimated within marker-defined subgroups. A marker will be dichotomized at the median if it takes continuous values. The difference in CR rates between subgroups will be estimated with 95% confidence intervals. If subgroups are of equal size, assuming a 50% overall CR rate, we have 80% power to detect a difference of 12.5% (56.2% vs. 43.7%) in CR rates between the subgroups with two-sided type I error rate of 0.05, if we have marker measurements for all 519 patients. If 80% of the patients (415 patients) have marker measurements, the difference we can detect is 14.2% (57.1% vs. 42.9%). A multivariate logistic regression model will be used to assess the effects of markers and clinical covariates on CR rates jointly.

PFS will be estimated within marker-defined subgroups with the Kaplan-Meier method, and 95% confidence intervals will be calculated at different time points. With a total of 519 patients and 203 events, we have 80% power to detect a hazard ratio of 1.49 between the subgroups with two-sided type I error rate of 0.05, assuming the two subgroups are of equal size. If 80% of the patients have marker measurements, the hazard ratio we can detect is 1.56, assuming the proportions of patients missing marker measurements are the same between events and censored cases. A multivariate Cox proportional hazards model will be used to assess marker and clinical covariate effects on PFS jointly.

MRD will be assessed by flow cytometry at the 12 month response evaluation in patients on both treatment arms as well as longitudinally in the Ibrutinib arm. The proportion of patients with an MRD negative remission at the time of the 12 month response evaluation will be compared across arms using two-sample binomial tests. Pair-wise comparisons of MRD levels at different time points within a given treatment arm will be made using the Wilcoxon signed-rank test to determine when MRD levels nadir for most patients.

We will use the landmark method [5] to assess the association between a particular MRD status time-point and outcome (PFS and OS). For each time point, only patients without a prior event and evaluated at that time will be included. Assuming that i) time to 25% patients dying is 62.5 months, ii) 90% patients have MRD measurements, and iii) the percentage of patients achieving MRD- status, being 60% for the FCR arm and 25% for the Ibrutinib arm, the hazard ratios in terms of PFS we can detect after 32 months of follow-up with 80% power and a two-sided type I error of 0.05 are 0.52, and 0.48, respectively, for the FCR arm and Ibrutinib arm. The MRD time point that is the most predictive of outcome is the one that gives the largest log-rank statistic by the landmark method. The performance of this predictor can be assessed by a cross-validation scheme, as described in Simon et al [1]. Cross-validated Kaplan-Meier curves will also be constructed and their significance computed by permutation. We will investigate whether a different threshold to classify MRD status at a given time-point provides a more accurate prediction of PFS using the same cross-validation strategy. Cross-validated ROC curves as well as the C-statistics will be used to summarize the performance of the predictors.

A joint longitudinal analysis of MRD levels will also be performed using random effects models described in Schluchter and Schluchter, Greene and Beck [3,4]. These account for informed missingness to assess treatment differences in the rate of change in the longitudinal analysis of MRD levels. The association of outcome (PFS) with MRD levels at the relevant time points will be explored using Andersen-Gill type of model with time-dependent covariates [7]. Similar modeling with relapse free survival as the outcome will be explored to understand how rising MRD levels post therapy predict relapse. Cross-validation will be used to evaluate prediction accuracy.

Effects of FCR and Ibrutinib-based therapy on T-cell immune function will be explored. We will measure T-cell counts and assess area of immune synapse at 12 months. Histograms of these counts will be plotted by arm. Medians will be compared using the Wilcoxon rank sum test. We will also measure T-cell immune repertoire, which will be explored using descriptive statistics.

The immune system will also be evaluated by Pneumococcal vaccination, administered to the first 100 patients on each arm at the 12-month response evaluation. Opsonophagocytic activity (OPA) titers against 6 pneumococcal serotypes will be measured pre-vaccination and on day 90 post vaccination. Overall Pnevna response (OPR) is defined as a 4-fold rise or more in geometric mean antibody titers for at least 4 of the 6 serotypes. Assuming an overall OPR rate of approximately 25% for the two arms, we have 80% power to detect a difference of 16% (FCR) vs. 34% (Ibrutinib) or more with a one-sided significance level of 0.025 using a two-sample binomial test. OPR rates will be estimated for the two arms with 95% confidence intervals.

We will build and evaluate a prognostic model that incorporates clinical and biological characteristics to predict response to therapy and clinical outcome. A 5-fold cross-validation scheme will be used. Patients will be randomly divided into five parts, four of which used for training and the remaining part used for testing. During the training stage, we will select important variables based on their p-values in Cox-proportional hazards models. A risk score and a classification rule can be developed from these variables. In the testing stage, the risk score is computed for patients in the test set and used to predict their clinical outcome.

Similarly, patients in the test set can also be classified to be responders or non-responders based on the classification rule. This process of training and testing can be repeated many times. The performance of the risk score and the classification rule can be evaluated using C-statistics and ROC curves.

Baseline and relapse samples will be collected to allow exploratory sequencing of Bruton's tyrosine kinase and downstream targets to study mechanisms of resistance to both FCR and Ibrutinib-based therapy. We will examine change across time from baseline to progression and explore clonal evolution, and epigenetic changes in methylation. Descriptive statistics will be used to find genes that play important roles in drug resistance.

9.8 Anticipated Accrual by Gender and Ethnicity

Based on previous data from E2997 the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	Gender		
	Females	Males	Total
Hispanic or Latino	2	5	7
Not Hispanic or Latino	151	361	512
Ethnic Category: Total of all subjects	153	366	519
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	7	7
Black or African American	17	48	65
Native Hawaiian or other Pacific Islander	0	0	0
White	136	311	447
Racial Category: Total of all subjects	153	366	519

9.9 Randomization Procedure

Patients will be randomized 2:1 to the Ibrutinib arm (A) and the FCR control arm (B) using permuted blocks with stratification and dynamic balancing on main institutions [6]. The stratification factors are age (<60 vs. ≥ 60), ECOG performance status (0/1 vs. 2), disease stage (3/4 vs. 1/2), and baseline cytogenetic abnormalities (deletion 11q23 vs. other).

9.10 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made

available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Center.

9.11 Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required.

References for Statistical Section:

1. Simon RM, Subramanian J, LI MC, Menezes S. Using cross-validation to evaluate predictive accuracy of survival risk classifiers based on high-dimensional data. *Brief Bioinform* 2011; 12(3): 203–214.
2. Hallek M, Fischer K, Fingerle-Rowson G, et al. (2010) Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*; 376(9747):1164-1174.
3. Schluchter MD (1992) Methods for the analysis of informatively censored longitudinal data. *Statistics in Medicine*; 11, 1861-1870.
4. Schluchter MD, Greene T and Beck GJ (2001) Analysis of change in the presence of informative censoring application to a longitudinal clinical trial of progressive renal disease. *Statistics in Medicine*; 20:989-1007.
5. Anderson JR, Cain KC, Gelber RD (1983) Analysis of survival by tumor response. *J Clin Oncol*. 1983;1:710-719.
6. Zelen M (1974) The randomization and stratification of patients to clinical trials. *Journal of Chronic Diseases*, 27:365-375.
7. Andersen PK & Gill RD. Cox's regression model for counting processes: a large sample study. *The annals of statistics*, 1982; 10(4), 1100-1120.
8. Freidlin, B., Korn, E. L., & Gray, R. (2010). A general inefficacy interim monitoring rule for randomized clinical trials. *Clinical Trials*, 7(3), 197-208.

10. Correlative Studies

NOTE: ECOG requires that all biological samples submitted be entered and tracked via the online ECOG Sample Tracking System. An STS shipping manifest form must be generated and shipped with the sample submissions. See Section [10.4](#).

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG Coordinating Center regarding logistics for submission of fresh samples.

NOTE: ECOG Institutions: Patients must be registered to E3903 Ancillary Laboratory Protocol for the Collection of Diagnostic Material on Patients Considered for ECOG Treatment Trials for Leukemia or Related Hematologic Disorders. If the patient is already registered to E3903, then the ECOG sequence number must be provided.

The above note does not apply to patients at Intergroup/CTSU institutions. E3903 is currently not open at the CTSU. Therefore, Intergroup/CTSU institutions are exempt from participating in E3903.

NOTE: If baseline specimens have been submitted via E3903 no additional baseline specimens are required for the studies outlined in Section [10.1](#), except for the bone marrow sections/slides. Additional specimens are requested for correlative studies as outlined in Section [10.2](#).

10.1 Immunophenotype and Molecular Genetics

Immunophenotyping has become an essential part of the diagnostic work-up of all leukemia patients. In fact, the diagnosis of leukemia without immunophenotypic characterization is no longer acceptable. ECOG has, therefore, developed a model system for antigenic data collection that requests specimens from all patients entered on ECOG leukemia treatment trials be studied by ECOG's Leukemia Translational Studies Laboratory (LTSL). In addition to establishing the leukemia subtype, this centralized testing and data collection has allowed that research questions of clinical relevance be applied to a growing database (e.g., definition of prognostically significant antigen expression levels to eventually yield specific treatment subcategories). Depending on the study protocol and tissue availability, anti-coagulated (heparin, EDTA, ACD) peripheral blood or bone marrow or both are to be submitted to the LTSL. The dual function of the LTSL in eligibility determination and sample processing/banking (ECOG's Leukemia Tissue Bank), facilitates the distribution of fresh or adequately processed specimens to other laboratories involved in protocol-embedded correlative studies, such as the analyses of epigenetic and genetic lesions.

In addition to the study of abnormal hematopoietic cells, the focus of research on circulating serum factors in patients with leukemia or myelodysplasia has increased. Two tubes of coagulated peripheral blood (red top tubes) are requested for future research studies that may aim at identifying pathogenetic, diagnostic, or prognostic factors associated with leukemia or myelodysplasia.

Serum and cells from peripheral blood or bone marrow from patients entered on studies of hematologic malignancies are stored in ECOG's Leukemia Tissue

Bank for future laboratory studies. The bank provides the scientific community a source of leukemia specimens that are collected, processed, and maintained following quality control and quality assurance guidelines. The bank will accommodate requests from investigators within and outside ECOG in a timely and efficient manner, with respect to tissue type, tissue preparation, and most importantly, biologic characteristics of specimens.

10.1.1 Sample Submission Schedule

All samples should be labeled with the ECOG protocol number E1912, the patient's initials, ECOG patient sequence number, date of collection, and type of sample (PB or BM).

- Peripheral blood and bone marrow/peripheral blood smears must be submitted at baseline for central review.
- Bone marrow sections/slides must be submitted at baseline and at the time of the twelve (12) month response evaluation for central histological review.

NOTE: Submission of pathology samples for central review is mandatory in order for the patient to be considered evaluable. Failure to submit pathology samples may render the case unevaluable.

- Buccal cells should be submitted at baseline for laboratory research studies.
- Peripheral blood should be submitted at baseline for banking.

NOTE: Dr. Paietta's institutional regulations require that she receive copies of patient consents and HIPAA authorization forms along with the baseline samples.

If you have any questions, please contact the LTSL at (718) 920-9992.

Biological Materials	Baseline ¹	Twelve (12) Month Response Evaluation (52 weeks after day 1 of cycle 1)
MANDATORY for Central Review		
Bone Marrow Sections/Slides	X	X
Bone Marrow/Peripheral Blood Smears (Wright-Giemsa stained) ²	X	
Peripheral Blood (heparin, (4) 10mL green or purple [EDTA] top tubes, 30-40mL) ²	X	
From Patients Who Answer "YES" to "I agree to participate in the laboratory research studies that are being done as part of this clinical trial."		
Buccal Swab or Rinse ²	X	
From Patients Who Answer "YES" to "I agree to provide additional blood for research."		
Peripheral Blood (serum, (2) 10mL red top tubes, 15-20mL) ²	X	

1. After randomization, prior to treatment.

2. If submitted as part of E3903 no additional samples are required on E1912.

10.1.2 Sample Preparation Guidelines

The following samples **must** be submitted:

- Heparinized or EDTA peripheral blood ([4] 10mL green or purple top tubes, 30-40mL)
- At least two (2) Wright-Giemsa stained bone marrow smears and one (1) Wright-Giemsa stained peripheral blood smear.
- Submit eight (8) unstained slides cut at five (5) microns. Label the slides with the ECOG patient sequence number, date of collection, and order of sections. Do not bake or place cover slips on the slides.

A copy of the institutional pathology report on the bone marrow must be submitted. If the pathology report is not available at the time the samples are mailed to the ECOG Leukemia Translational Studies Laboratory, the report must be faxed at a later time to: (718) 920-1161.

10.1.2.1 The following should be submitted at baseline to be banked for use in future studies:

- Two (2) 10mL red top serum tubes of peripheral blood (15-20mL)

NOTE: If samples designated for banking only are not submitted, please note the reason in the Comments section of the Sample Tracking System.

10.1.2.2 The following should be submitted at baseline to be used in the laboratory research studies:

- Buccal Cell Samples

Most commonly, institutions will have buccal swab kits for the collection of cells for HLA-typing. However, should an institution inform the Leukemia Tissue Bank that buccal swab kits are not part of their regular supplies; it will be recommended to use Scope, a commercial brand mouthwash, or normal saline in a small sealed bottle.

- Aseptic techniques must be used to collect buccal cells from patients on-site and buccal cells must not be contaminated with cells from any other source. Patients should not brush their teeth or consume food prior to buccal cell collection.
- If a cytobrush is used, the collection end should not be touched and the patient should not scrape his/her cheek too vigorously. The inside of the cheek should be scraped 6 times. Several models of cytobrushes are available, such as the Omni swab or Bio-Swab from Arrowhead Forensics or the Cyto-Pak CytoSoft Brush from Medical Packaging Corp.
- If mouthwash or normal saline is used, the patient should pour approximately 10cc of mouthwash or

saline into his/her mouth and vigorously swish it against the cheeks for 10 seconds and deliver the solution with a sterile beverage straw into a labeled 15cc polypropylene test tube. Among mouthwashes, the Scope brand fares best in collecting buccal cells for the preparation of high-quality DNA in high yield.

It is important that buccal cells do not dry out during shipping. Institutions are advised to seal the container containing the buccal cells tightly. Ship containers on ice-packs, together with the patient's peripheral blood.

10.1.3 Shipping Procedures

Log the shipment into the ECOG STS the day of shipment. If the STS is unavailable, an ECOG Generic Specimen Submission Form (#2981) must be submitted with the samples. Once STS is available, retroactively log the shipment into STS, using the actual collection and shipping dates.

The LTSL must be notified by telephone, 24 hours prior to the arrival of the samples.

Fax is not acceptable.

Telephone: (718) 920-9992 Beeper (off hours): (917) 729-7231

If you want to notify the laboratory of a sample submission during off hours, please leave a message on the laboratory's answering machine (718-920-9992). Page Dr. Paietta at the beeper number above only if there are questions regarding the sample submission.

The bone marrow sections/slides should be submitted within one month of collection.

Peripheral blood, serum and buccal cells must be sent fresh (on the day of collection) on cool packs (do not freeze and do not use ice cubes) by overnight courier (preferably Federal Express) to arrive within 24 hours to:

Elisabeth Paietta, Ph.D.
Montefiore North Division
Cancer Center
600 East 233rd Street
Bronx, New York 10466
Tel: (718) 920-9992
Fax: (718) 920-1161
E-mail: epaietta@earthlink.net

An STS shipping manifest form must be generated and shipped with all sample submissions.

The LTSL is open to receive shipments Monday through Saturday. Shipments on Fridays for Saturday delivery must have "Saturday Delivery" marked on the overnight courier slip.

If samples need to be drawn late at night, on Sunday, or on a holiday when Federal Express does not operate, keep the samples in a

refrigerator between 10 and 15 degrees Celsius until the next day when it can be shipped.

10.1.3.1 Sample Processing and Routing

Bone marrow sections/slides will be forwarded to Dr. Curtis Hanson at Mayo Clinic for central histological review,

10.2 Submissions to Mayo Clinic for Correlative Studies

All samples should be labeled with the ECOG protocol number E1912, the patient's initials, ECOG patient sequence number, and date of collection.

Participating institutions can order kits by contacting Charla Secreto at (507) 284-3805. The appropriate type and number of collection tubes will be contained within each kit, along with the Federal Express air bill.

10.2.1 Sample Submission Schedule

Peripheral blood samples are requested at the intervals indicated below.

Biological Materials	Baseline ¹	After Three (3) Cycles of Therapy	After Six (6) Cycles of Therapy [Prior to Cycle Seven (7) Arm A, End of Cycle Six (6) Arm B]	Twelve (12) Month Response Evaluation (52 weeks after day 1 of cycle 1)	18, 24, and 36 Months After Randomization	Time of Disease Progression or Relapse
From Patients Who Answer "YES" to "I agree to participate in the laboratory research studies that are being done as part of this clinical trial."						
Peripheral Blood (sodium heparin (5) 10mL green top tubes)	X	X	X	X	X	X
Peripheral Blood (serum, (2) 10mL red top tubes)	X			X		

1. After randomization, prior to treatment.

NOTE: For patients who consent to the correlative studies, please submit ALL sequential blood samples at ALL time points.

10.2.2 Shipping Procedures

Log the shipment into the ECOG STS the day of shipment. If the STS is unavailable, an ECOG Generic Specimen Submission Form (#2981) must be submitted with the samples along with the Patient Information Form, [Appendix I](#). Once STS is available, retroactively log the shipment into STS, using the actual collection and shipping dates.

Please include CBC and differential information (WBC and % lymphocytes) with each blood sample, if available, via the Sample Tracking System.

Place filled tubes in a styrofoam container with absorbent material and put in corrugated mailer box. Follow the packing guidelines listed in the kit.

Peripheral blood samples should be sent fresh, the day of collection, on cool packs (do not freeze) and shipped overnight to arrive during normal working hours.

Ship Monday – Thursday only. The laboratory is open to receive shipments Monday through Friday.

FRIDAY AND PREHOLIDAY SHIPMENTS SHOULD BE AVOIDED

Please call Charla Secreto at (507) 284-3805 when the blood samples are being shipped.

Ship to:

Charla Secreto
Mayo Clinic
613 Stabile
200 First Street, SW
Rochester, MN 55905

An STS shipping manifest form must be generated and shipped with all sample submissions.

Blood samples will be forwarded to Dr. Curtis Hanson at Mayo Clinic for analysis as described in Section [10.3](#).

10.3 Studies to be performed:

10.3.1 IGHV Mutation Analysis

The IGHV mutation status will be assessed at baseline to allow exploration of how IGHV mutation status correlates with clinical outcomes (CR, PFS) of the different treatment arms.

10.3.2 Minimal Residual Disease Assessment by Flow Cytometry

MRD status will be assessed in patients on both treatment arms at the time of the 12 month response evaluation (52 weeks after day 1 of cycle 1) to determine the ability of this conventional MRD time-point to predict clinical outcome (PFS, OS). Blood samples for MRD assessment by flow cytometry will also be collected on both treatment arms 24 and 36 months from randomization. An early MRD assessment is also planned at 3 months in the FCR arm of the study.

Although samples will be collected and archived from all time-points in patients on both treatment arms, the initial planned MRD assessments at these other time-points will be tailored to address hypotheses specific to each arm. The initial planned time-points of assessment are:

MRD assessment time-points	3 mo	12 mo	24 mo	36 mo
FCR (Arm B)	X	X	X	X
Ibrutinib/rituximab (Arm A)		X	X	X

As noted, this plan will include assessment of MRD status after the first 3 cycles of FCR in arm B to confirm studies suggesting that ~25% of patients achieve an MRD negative disease state after 3 cycles of FCR.

Although a sample to permit MRD assessment at that time-point will also be collected for patients on the Ibrutinib arm, it is expected nearly all patients treated with Ibrutinib/rituximab have overt residual disease after only 3 months of therapy. Collectively, these longitudinal studies of MRD on both treatment arms will allow better characterization of when MRD levels nadir and help define the optimal timing of MRD assessment for both treatment approaches.

10.3.3 Genetic studies:

DNA (germline and tumor cell) will also be collected at baseline and longitudinally to evaluate the association of genetic mutations in leukemic cells (clonal or sub-clonal) at baseline and during treatment with subsequent response to treatment using CIT and non-CIT approaches.

10.3.4 B-cell receptor Signaling:

Blood cells will be collected at baseline and during treatment to evaluate signaling networks downstream of the B-cell receptor to help better define the mechanism of action (and potential mechanisms of resistance) to Ibrutinib based therapy.

10.3.5 Pharmacogenetics Studies:

DNA (germline) will also be collected at baseline to allow confirmatory genotyping of single nucleotide polymorphism associated with the efficacy and toxicity of fludarabine-based therapy in a prior ECOG GWAS analysis. DNA (both tumor and germline) will also be collected for exploratory GWAS studies to identify genetic characteristics associated with the efficacy and toxicity of sensitivity to Ibrutinib based therapy.

10.3.6 Thymidine Kinase:

Serum samples will be collected to allow assessment of baseline Thymidine Kinase levels.

10.3.7 T-Cell Studies:

Blood samples will be collected after 3 cycles of therapy, after 6 cycles of therapy, at the time of the twelve (12) month response

evaluation, and during later follow-up to assess immune function including assessment of quantitative T-cell counts, T-cell repertoire, and T-cell function (immune synapse). Serum and plasma will also be collected at these time points to allow evaluation of immune cytokines.

- 10.3.8 Drug Resistance: Leukemia samples at the time of relapse or progression will be collected to allow biologic studies exploring the mechanisms of resistance to both fludarabine and Ibrutinib based therapy

10.4 ECOG Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG Sample Tracking System (STS). The software will allow the use of either 1) an ECOG user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking <https://webapps.ecog.org/Tst>

Important: Any case reimbursements associated with samples submissions will not be credited if samples are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: <http://www.ecog.org/general/stsinfo.html> Please take a moment to familiarize yourself with the software prior to using the system.

A shipping manifest form must be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

Study Specific Notes

ECOG Generic Specimen Submission Form (#2981) will be required only if STS is unavailable at time of sample submission, along with the Patient Information Form ([Appendix I](#)). Indicate the appropriate Lab ID# on the submission form:

- 0002 = ECOG Leukemia Translational Studies Laboratory
- 0156 = Mayo Clinic Hematology Research Laboratory

Retroactively enter all specimen collection and shipping information when STS is available.

10.5 Banking

The residuals and/or derivatives of the bone marrow and peripheral blood samples collected for this study will be retained at the ECOG Leukemia Translational Studies Laboratory/ECOG Leukemia Tissue Bank for possible use in ECOG approved future studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

10.6 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used will be submitted electronically via secure web application to the ECOG Coordinating Center on a monthly basis or upon request by any laboratory holding and/or using any specimens associated with this study.

10.7 Lab Data Transfer Guidelines

The data collected or generated on the above mentioned correlative studies will be submitted electronically via secure data portal to the ECOG Coordinating Center by the central laboratory on a quarterly basis.

11. Records to Be Kept

Please refer to the **E1912** Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG Coordinating Center to CTEP by electronic means.

11.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG Coordinating Center prior to destroying any source documents.

12. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

13. References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA: a cancer journal for clinicians*. 2011;61(2):69-90. Prepublished on 2011/02/08 as DOI 10.3322/caac.20107.
2. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008;111(12):5446-5456.
3. Shanafelt TD, Rabe KG, Kay NE, et al. Age at diagnosis and the utility of prognostic testing in patients with chronic lymphocytic leukemia. *Cancer*. 2010.
4. Call T, Phylky R, Noel P, et al. Incidence of chronic lymphocytic leukemia in Olmsted County, Minnesota, 1935 through 1989, with emphasis on changes in initial stage at diagnosis. *Mayo Clinic Proceedings*. 1994;69:323-328.
5. Cavotky D, Fooks J, Richards S. Prognostic factors in chronic lymphocytic leukaemia: the importance of age, sex and response to treatment in survival. *Br J Haematol*. 1989;72:141-149.
6. Dighiero G, Maloum K, Desablens B, et al. Chlorambucil in indolent chronic lymphocytic leukemia. *Frech Cooperative Group on Chronic Lymphocytic Leukemia*. *N Engl J Med*. 1998;338:1506-1514.
7. Diehl LF, Karnell LH, Menck HR. The American College of Surgeons Commission on Cancer and the American Cancer Society. The National Cancer Data Base report on age, gender, treatment, and outcomes of patients with chronic lymphocytic leukemia. *Cancer*. 1999;86(12):2684-2692.
8. Molica S, Levato D, Dattilo A. Natural history of early chronic lymphocytic leukemia. A single institution study with emphasis on the impact of disease-progression on overall survival. *Haematologica*. 1999;84(12):1094-1099.
9. Molica S, Levato D. What is changing in the natural history of chronic lymphocytic leukemia. *Haematologica*. 2001;86:8-12.
10. Flinn IW, Neuberg DS, Grever MR, et al. Phase III trial of fludarabine plus cyclophosphamide compared with fludarabine for patients with previously untreated chronic lymphocytic leukemia: US Intergroup Trial E2997. *J Clin Oncol*. 2007;25(7):793-798.
11. Eichhorst BF, Busch R, Hopfinger G, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. *Blood*. 2006;107(3):885-891.
12. Catovsky D, Richards S, Matutes E, et al. Fludarabine Plus Cyclophosphamide Improves Response and Progression-Free Survival in Chronic Lymphocytic Leukemia. A Report from the LRF CLL4 Trial. *Lancet*. 2007;370:230-239.
13. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376(9747):1164-1174.

14. Tam CS, O'Brien S, Wierda W, et al. Long term results of the fludarabine, cyclophosphamide & rituximab regimen as initial therapy of chronic lymphocytic leukemia. *Blood*. 2008.
15. Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. *Blood*. 2007;109(2):405-411.
16. Keating M, O'brien S, Albitar M, et al. Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab as Initial Therapy for Chronic Lymphocytic Leukemia. *J Clin Oncol*. 2005;23:4079-4088.
17. Ferrajoli A, O'Brien S M, Wierda W, al e. Treatment of patients with CLL 70 years old and older: a single center experience of 142 pateints. *Leuk Lymphoma*. 2005;46(S86).
18. Bosch F, Abrisqueta P, Villamor N, et al. Rituximab, Fludarabine, Cyclophosphamide, and Mitoxantrone a New, Highly Active Chemoimmunotherapy Regimen for Chronic Lymphocytic Leukemia. *J Clin Oncol*. 2009.
19. Wierda W, O'Brien SM, Faderl S, et al. CFAR, an active frontline regimen for high-risk patients with CLL, including those with Del 17p. *Blood*. 2008;112:2095(abstract).
20. Stevenson FK, Krysov S, Davies AJ, Steele AJ, Packham G. B-cell receptor signaling in chronic lymphocytic leukemia. *Blood*. 2011;118(16):4313-4320. Prepublished on 2011/08/06 as DOI 10.1182/blood-2011-06-338855.
21. Friedberg JW, Sharman J, Sweetenham J, et al. Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Blood*. 2010;115(13):2578-2585. Prepublished on 2009/12/08 as DOI 10.1182/blood-2009-08-236471.
22. Furman R, Byrd JC, Brown JR, et al. CAL-101, An Isoform-selective inhibitor of phosphatidylinositol 3-Kinase P110d, demonstrates clinical activity and pharmacodynamic effects in patients with relapsed or refractory chronic lymphocytic leukemia. *Blood*. 2010;116:Abstract #55.
23. Zent CS, LaPlant BR, Johnston PB, et al. The treatment of recurrent/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) with everolimus results in clinical responses and mobilization of CLL cells into the circulation. *Cancer*. 2010;116(9):2201-2207. Prepublished on 2010/02/19 as DOI 10.1002/cncr.25005.
24. Mohamed AJ, Yu L, Backesjo CM, et al. Bruton's tyrosine kinase (Btk): function, regulation, and transformation with special emphasis on the PH domain. *Immunological reviews*. 2009;228(1):58-73. Prepublished on 2009/03/18 as DOI 10.1111/j.1600-065X.2008.00741.x.
25. Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by Ibrutinib. *Blood*. 2011;117(23):6287-6296. Prepublished on 2011/03/23 as DOI 10.1182/blood-2011-01-328484.
26. Shanafelt TD, Bowen D, Venkat C, et al. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. *British Journal of Haematology*. 2007;39:255-264.

27. Else M, Smith AG, Cocks K, et al. Patients' experience of chronic lymphocytic leukaemia: baseline health-related quality of life results from the LRF CLL4 trial. *British Journal of Haematology*. 2008;143(5):690-697. Prepublished on 2008/11/20 as DOI 10.1111/j.1365-2141.2008.07407.x.
28. Eichhorst BF, Busch R, Obwandner T, Kuhn-Hallek I, Herschbach P, Hallek M. Health-Related Quality of Life in Younger Patients With Chronic Lymphocytic Leukemia Treated With Fludarabine Plus Cyclophosphamide or Fludarabine Alone for First-Line Therapy: A Study by the German CLL Study Group. *J Clin Oncol*. 2007.
29. Levy V, Porcher R, Delabarre F, Leporrier M, Cazin B, Chevret S. Evaluating treatment strategies in chronic lymphocytic leukemia: use of quality-adjusted survival analysis. *J Clin Epidemiol*. 2001;54(7):747-754.
30. Eichhorst BF, Busch R, Stilgenbauer S, et al. First line therapy with fludarabine compared to chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. *Blood*. 2009.
31. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol*. 1999;17(12):3835-3849.
32. Rawstron AC, Villamor N, Ritgen M, et al. International Standardized Approach for Flow Cytometric Residual Disease Monitoring in Chronic Lymphocytic Leukemia. *Blood*. 2006;In Press.

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).**Appendix I****Patient Information Form**

It is required that samples submitted from patients participating in E1912 be entered and tracked via the online ECOG Sample Tracking System (see Section [10.4](#)). This form is used only in the event that the STS is inaccessible and then the shipments are to be logged in retroactively, indicating the actual dates of collection and shipment.

PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND PREHOLIDAYSECOG Protocol #: **E1912** ECOG Sequence #: _____ Patient Initials: _____

Specimen Date: _____ Time Drawn: _____

Physician: _____ Institution/Affiliate: _____

Contact /Coordinating Person:

Name: _____ Phone#: _____

Address: _____

City, State, Zip: _____

PLEASE INCLUDE CURRENT WHITE BLOOD COUNT AND DIFFERENTIAL:

WBC _____ LYMPHOCYTE % _____

Study Time Point Circle Below:

1. Baseline
2. After three (3) cycles
3. After six (6) cycles
4. At time of response evaluation
5. At 18, 24 and 36 months post randomization
6. Other _____

Any questions concerning these blood samples or to order collection kits please contact: Charla Secreto, Hematology Research, Tel: (507) 284-3805.

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).**Appendix II****Patient Thank You Letter**

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at <http://www.ecog.org>. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME]

[DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of **[INSTITUTION]** and the Eastern Cooperative Oncology Group, we thank you again.

Sincerely,

[PHYSICIAN NAME]

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).

Appendix III

Ibrutinib Patient Medication Calendar

Ibrutinib should be taken with 8 ounces of water.

Pill Calendar Directions

1. Take your scheduled dose of each capsule.
2. If you forget, the missed capsules will not be taken later.
3. Please bring the empty bottle or any leftover capsules and your medication calendar to your next clinic visit.

Ibrutinib Patient Medication Calendar

This is a calendar on which you are to record the time and number of capsules you take each day. You should take your scheduled dose of each capsule. **Note the times and the number of capsules that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused capsules and your completed medications calendar to your doctor’s visits.

DAY	Date			Time capsules taken		Number of capsules taken		Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year	AM	PM	AM	PM	
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
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E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).**Appendix IV****CRADA/CTA**

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (<http://ctep.cancer.gov/industry>) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: <http://ctep.cancer.gov>.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):
 - a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
 - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
 - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX 301-402-1584
Email: anshers@ctep.nci.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).**Appendix V****ECOG Performance Status**

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 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.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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Appendix VI

Grading Scale for Hematologic Toxicity in CLL Studies

Decrease from Pretreatment value (%)	Grade ²	
	Platelets ^{3,5}	Hemoglobin ^{4,5}
No change - 10%	0	0
11-24%	1	1
25-49%	2	2
50-74%	3	3
≥ 75%	4	4

1. A decrease in circulating granulocytes is not being considered since it is not a reliable index in CLL.
2. Grades: 1–mild; 2–moderate; 3–severe; 4–life–threatening. Grade 5 (fatal) toxicity can potentially occur at any level of decrease from pretreatment values and will be recorded as such.
3. If, at any level of decrease the platelet count is < 20,000/μL, this will be considered grade 4, unless the initial platelet count was ≤ 20,000 μL in which case the patient is inevaluable for toxicity referable to platelet counts.
4. Baseline and subsequent hemoglobin determinations must be immediately prior to any given transfusions.
5. If, at any level of decrease from the baseline value the platelet and/or hemoglobin counts are within normal limits, this will be considered a grade 0.

Hallek BD, et al.: Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer-Institute- Working Group 1996 guidelines: Blood 111:54465456, 2008.

Hematologic Toxicity Grading Worksheet

<u>Decrease in platelets or hemoglobin from pretreatment value</u>	<u>Grade</u>	<u>Platelets</u>	<u>Hemoglobin</u>
Baseline			
No Change – 10%	0		
11 – 24%	1		
25 – 49%	2		
50 – 74%	3		
≥ 75%	4		

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).

Appendix VII

Cumulative Illness Rating Scale

Rating Strategy of Comorbidity		
0	No problem	Organ system not compromised.
1	Mild	Illness/impairment with or without requirement of therapy, excellent prognosis, patient with normal activity.
2	Moderate	Illness/impairment requiring therapy, good prognosis, comprised activity of patient.
3	Severe	Illness/impairment with urgent requirement of therapy, prognosis unclear, marked restriction in activity.
4	Extremely severe	Life threatening illness/impairment, emergency case of therapy, adverse prognosis.

Please take into account that CLL induced illness or organ damage are not included in this rating scale! The goal of this rating scale is to assess comorbidity other than CLL in the patient. If there are two or more illnesses/impairments of one organ system, the illness/impairment with the highest severity should be evaluated!

Organ System	A) If illness/impairment present, please specify	B) Score
1. Heart		<input type="checkbox"/>
2. Blood pressure		<input type="checkbox"/>
3. Vascular		<input type="checkbox"/>
4. Respiratory		<input type="checkbox"/>
5. Ear/nose/throat		<input type="checkbox"/>
6. Upper gastrointestinal		<input type="checkbox"/>
7. Lower gastrointestinal		<input type="checkbox"/>
8. Liver		<input type="checkbox"/>
9. Renal		<input type="checkbox"/>
10. Genitourinary		<input type="checkbox"/>
11. Musculoskeletal		<input type="checkbox"/>
12. Endocrine/metabolic		<input type="checkbox"/>
13. Neurological		<input type="checkbox"/>
14. Psychiatric		<input type="checkbox"/>
15. Score:	Total	<input type="checkbox"/> <input type="checkbox"/>

Extermann et al JCO 16: 1582–1587,

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).

Appendix VIII

CYP3A 4/5 Inhibitors and Inducers

The medications or substances that are listed in the table below are **strong or moderate inhibitors** of CYP3A4.

Strong and moderate inhibitors of CYP3A4/5 should also be avoided while taking ibrutinib.

If patients require treatment with strong or moderate inhibitors of CYP3A4 that are used after registration see Section [8.1.11](#) for additional information on monitoring and Ibrutinib dosing. A comprehensive list of inhibitors, inducers, and substrates may be found at <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>. This website is continually revised and should be checked frequently for updates.

<p>Strong Inhibitors of CYP3A4/5 > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance</p> <p>Boceprevir (Victrelis®) Clarithromycin (Biaxin®, Biaxin XL®) Conivaptan (Vaprisol®) Grapefruit juice Indinavir (Crixivan®) Itraconazole (Sporanox®) Ketoconazole (Nizoral®) Lopinavir/Ritonavir (Kaletra®) Mibefradil Nefazodone (Serzone®) Nelfinavir (Viracept®) Posaconazole (Noxafil®) Ritonavir (Novir®, Kaletra®) Saquinavir (Fortovase®, Invirase®) Telaprevir (Incivek®) Telithromycin (Ketek®) Voriconazole (Vfend®)</p>
<p>Moderate Inhibitors of CYP3A4/5 > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance</p> <p>Amprenavir (Agenerase®) Aprepitant (Emend®) Atazanavir (Reyataz®) Ciprofloxacin (Cipro®) Darunavir (Prezista®) Diltiazem (Cardizem®, Cardizem CD®, Cardizem LA®, Cardizem SR®, Cartia XT™, Dilacor XR®, Diltia XT®, Taztia XT™, Tiazac®) Erythromycin (Erythrocin®, E.E.S.®, Ery-Tab®, Eryc®, EryPed®, PCE®) Fluconazole (Diflucan®) Fosamprenavir (Lexiva®) Imatinib (Gleevec®) Verapamil (Calan®, Calan SR®, Covera-HS®, Isoptin SR®, Verelan®, Verelan PM®)</p>

Weak Inhibitors of CYP3A4

> 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance

Alprazolam
 Amiodarone
 Celecoxib
 Chloramphenicol
 Cimetidine (Tagamet®, Tagamet HB 200®)
 Desvenlafaxine
 Diltiazem
 Diphenhydramine
 Echinacea
 Escitalopram
 Febuxostat
 Gefitinib
 Hydralazine
 Hydroxychloroquine
 Imatinib
 Methadone
 Oral contraceptives
 Propafenone
 Ranitidine
 Ritonavir
 Sertraline
 Telithromycin
 Verapamil

Receiving any medications or substances that are **inducers** of CYP3A4.

Use of the following inducers are prohibited ≤ 7 days prior to registration.

Strong Inducers of CYP3A4/5

> 80% decrease in AUC

Avasimibe
 Carbamazepine (Carbatrol®, Epitol®, Equetro™, Tegretol®, Tegretol-XR®)
 Phenytoin (Dilantin®, Phenytek®)
 Rifampin (Rifadin®)
 St. John's wort

Moderate Inducers of CYP3A4/5

50-80% decrease in AUC

Bosentan (Tracleer®)
 Efavirenz (Sustiva®)
 Etravirine (Intelence®)
 Modafinil (Provigil®)
 Nafcillin
 Nevirapine (Viramune®)
 Phenobarbital (Luminal®)
 Rifabutin (Mycobutin®)
 Troglitazone

Weak Inhibitors of CYP3A4

20-50% decrease in AUC

Amprenavir (Agenerase®)
 Aprepitant (Emend®)
 Armodafinil
 Echinacea
 Pioglitazone (Actos®)
 Prednisone
 Rufinamide (Banzel®)

INHIBITORS OF CYP3A4/5:

1. use of strong CYP3A4/5 inhibitors (such as indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, ketoconazole, itraconazole, and nefazodone) should be avoided while on Ibrutinib.
2. Moderate CYP3A4/5 inhibitors (aprepitant, erythromycin, fluconazole, verapamil, and diltiazem) should be used with caution while on Ibrutinib.
3. Grapefruit juices and Seville oranges may also increase Ibrutinib plasma concentrations and should be avoided for the duration of Ibrutinib treatment.

For Patient Use While Taking Ibrutinib (PCI-32765)**INFORMATION ON POSSIBLE DRUG INTERACTIONS**

You are enrolled on a clinical trial using the experimental agent _____ . This clinical trial is sponsored by the NCI. _____ interacts with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.
- Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial.
- You should avoid supplements such as fish oils and vitamin E; check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

_____ interacts with a specific liver enzyme called **CYP**_____, and must be used very carefully with other medicines that interact with this enzyme.

- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP**_____."
- Before prescribing new medicines, your regular prescribers should go to <http://medicine.iupui.edu/clinpharm/ddis/table.aspx> for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).**Appendix IX****Instructions for Reporting Pregnancies on a Clinical Trial****What needs to be reported?**

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on Ibrutinib, or within 28 days of the patient's last dose of Ibrutinib must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via NCI's Adverse Event Expedited Reporting System (AdEERS)

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited AdEERS report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the AdEERS report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the AdEERS report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via AdEERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG Coordinating Center. Please contact the ECOG Coordinating Center to ask for a conference call to be set up with the appropriate individuals.
- It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial AdEERS report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* AdEERS report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the NCI Medical Help Desk at 301-897-7497 or adeersmd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Fetal Death

A fetal death is defined in CTCAE as “A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation.”

It must be reported via AdEERS as Grade 4 “Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)” under the System Organ Class (SOC) “Pregnancy, puerperium and perinatal conditions”.

A fetal death should **NOT** be reported as a Grade 5 event as currently AdEERS recognizes this event as a patient’s death.

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as “A disorder characterized by cessation of life occurring during the first 28 days of life” that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via AdEERS AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to lbrutinib must also be reported via AdEERS.

It must be reported via AdEERS as Grade 4 “General disorders and administration - Other (neonatal loss)” under the System Organ Class (SOC) “General disorder and administration”.

A neonatal death should **NOT** be reported as a Grade 5 event as currently AdEERS recognizes this event as a patient’s death.

Additional Required Forms:

When submitting AdEERS reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP 'Pregnancy Information Form'** must be completed and faxed along with any additional medical information to CTEP (301-230-0159). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).**Appendix X****Timed Up and Go (TUG) Test^{1,2}**

1. Equipment: arm chair, tape measure, tape, stop watch.
2. Begin the test with the subject sitting correctly in a chair with arms, the subject's back should resting on the back of the chair. The chair should be stable and positioned such that it will not move when the subject moves from sitting to standing.
3. Place a piece of tape or other marker on the floor 3 meters away from the chair so that it is easily seen by the subject.
4. Instructions: "On the word GO you will stand up, walk to the line on the floor, turn around and walk back to the chair and sit down. Walk at your regular pace.
5. Start timing on the word "GO" and stop timing when the subject is seated again correctly in the chair with their back resting on the back of the chair.
6. The subject wears their regular footwear, may use any gait aid that they normally use during ambulation, but may not be assisted by another person. There is no time limit. They may stop and rest (but not sit down) if they need to.
7. Normal healthy elderly usually complete the task in ten seconds or less. Very frail or weak elderly with poor mobility may take 2 minutes or more.
8. The subject should be given a practice trial that is not timed before testing.
9. Results correlate with gait speed, balance, functional level, the ability to go out, and can follow change over time.
10. Interpretation ≤ 10 seconds = normal
 ≤ 20 seconds = good mobility, can go out alone, mobile without a gait aid.
 < 30 seconds = problems, cannot go outside alone, requires a gait aid.

A score of more than or equal to fourteen seconds has been shown to indicate high risk of falls.

1. Podsiadlo D, Richardson S. *The Time "Up & Go": A Test of Basic Functional Mobility for Frail Elderly Persons*. Journal of the American Geriatrics Society 1991; 39(2): 142-148
2. Shumway - Cook A, Brauer S, Woollacott M. *Predicting the Probability for Falls in Community-Dwelling Older Adults Using the Timed Up & Go Test*. Physical Therapy 2000 Vol 80(9): 896-903.
Saskatoon Falls Prevention Consortium, Falls Screening and Referral Algorithm, TUG, Saskatoon Falls Prevention consortium, June, 2005

Rev. 3/14

This is an FDA Registration Trial

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL)

Rev. 7/14

STUDY CHAIR: Tait Shanafelt, M.D.
 ECOG CO-CHAIR: Neil Kay, M.D.
 SWOG CO-CHAIR: Susan O'Brien, M.D.
 CALGB CO-CHAIR: Jacqueline Barrientos, M.D.
 STUDY STATISTICIAN: Victoria Wang, PhD
 LEUKEMIA COMMITTEE CHAIR: Martin Tallman, M.D.
 PATIENT OUTCOMES AND SURVIVORSHIP CHAIRS: Lynne Wagner, PhD
 Mary Thomas, RN, MS, AOCN
 PATHOLOGY CO-CHAIR: Curtis Hanson, M.D.
 LABORATORY CO-CHAIR: Curtis Hanson, M.D.

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STUDY PARTICIPANTS

SWOG / SWOG
ALLIANCE / Alliance for Clinical Trials in Oncology
CCTG / Canadian Cancer Trials Group
NRG / NRG Oncology

ACTIVATION DATE

January 31, 2014
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Agent	IND#	NSC#	Supply
Ibrutinib	117241	748645	NCI
Fludarabine		312887	Commercial
Cyclophosphamide		26271	Commercial
Rituximab		687451	Commercial

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STUDY CHAIR

Tait Shanafelt, M.D.
Mayo Clinic
200 First Street
Rochester, MN 55902
Telephone: 507-538-0591
Fax: 507-266-4972
E-mail: Shanafelt.Tait@mayo.edu

ECOG-ACRIN CO-CHAIR

Neil E. Kay, M.D.
Mayo Clinic
200 First Street SW
Rochester, MN 55905
Telephone: 507-284-1961
Fax: 507-266-9277
E-mail: Kay.Neil@mayo.edu

STUDY CHAIR LIAISON (SCL)

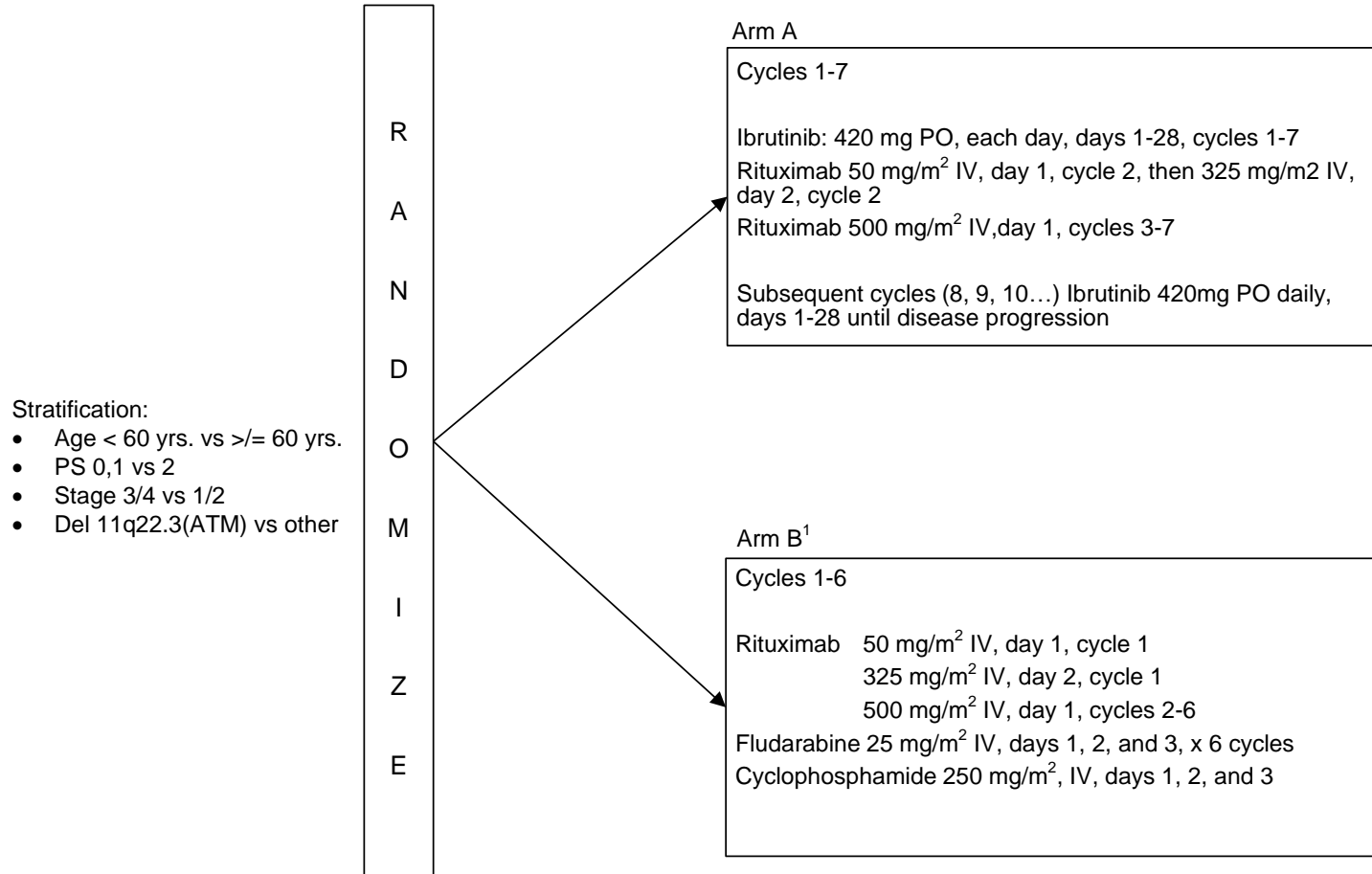
Tami Simmons
Division of Hematology
Mayo Clinic
W-10 Mayo Building
200 First Street SW
Rochester, MN 55905
Telephone: 507-284-4740
E-mail: simmons.tamera@mayo.edu

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	For patient enrollments:	Submit study data
<p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.cocccg.org (for submitting regulatory documents only)</p>	<p>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.</p> <p>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</p>	<p>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to the CTSU Data Operations. Do not copy the CTSU on data submissions.</p>
<p>The most current version of the study protocol and supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.</p>		
<p><u>For clinical questions (i.e. patient eligibility or treatment-related)</u> contact the Study PI of the Coordinating Group.</p>		
<p><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p>The CTSU Web site is located at https://www.ctsu.org</p>		

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Schema



Accrual: 519
Cycle length = 28 days

1. Arm B – Sequence of drug administration is rituximab, then fludarabine, then cyclophosphamide. See Section 5.1.3.

1. Introduction

1.1 Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is one of the most common lymphoid malignancies, accounting for ~11% of all hematologic neoplasms.¹ CLL affects approximately 100,000 individuals in the United States (~15,000 new cases/year) and is currently an incurable disease.^{1,2} While a majority of patients with CLL have early stage disease at diagnosis ~70% eventually progress to require treatment and a majority will ultimately die from CLL or CLL related complications.³⁻⁹

The last 2 decades have been a time of tremendous advances in the treatment of patients with CLL. During this interval, randomized trials have established that single agent fludarabine is superior to single agent alkylator-based approaches and demonstrated that combination of fludarabine and cyclophosphamide improves response rates and progression free survival (PFS) for younger CLL patients.¹⁰⁻¹² More recently, the addition of rituximab to purine nucleoside analogue-based chemotherapy has been shown to not only improve response rates and PFS but to also prolong overall survival in patients with CLL.

Despite the improved efficacy of CIT, only 40-45% of patients treated with these approaches currently achieve a CR and nearly all patients (including those achieving CR) eventually relapse.¹³⁻¹⁵ Although they are not curative, aggressive fludarabine based CIT regimens also result in substantial toxicity including profound immunosuppression, prolonged cytopenias (which can restrict salvage therapy options at the time of recurrence), and a 5-10% risk of therapy-related myelodysplasia (MDS).^{14, 16, 17} These toxicities are particularly problematic since nearly all CLL patients are >age 50 at diagnosis and many patients have coexistent health problems that limit their ability to receive CIT.¹³ Even among younger, fit CLL patients >25% are unable to tolerate FCR-based CIT, where previous phase 3 trial indicate that 56% of patients experience grade 3-4 myelosuppression, 25% an infectious complication, and 47% require dose reductions.¹³ Even with these extensive dose reductions, >25% of patients are unable to complete the intended 6 cycles of FCR induction.¹³ The end result is that, while FCR has been a major advance in the CLL treatment, it is associated with profound toxicity that limits the benefit of this approach for many patients.

These facts continue to foster interest in identifying novel approaches to improve both the efficacy and tolerability of CLL therapy. Although pilot studies have explored intensification approaches adding additional cytotoxic agents to CIT in an effort to improve efficacy (e.g. FCRM, CFAR, OFAR), the substantial toxicity of standard CIT renders these intensification approaches unfeasible for most CLL patients.^{18, 19}

While new combinations of existing/traditional chemotherapeutic agents may lead to incremental progress in CLL treatment, more substantive improvements will likely occur through therapeutic targeting of novel biologic pathways critical to the survival and/or chemotherapy resistance of CLL B-cells. A profound increase in the understanding of CLL B-cell biology over the last decade has identified numerous potential therapeutic targets. In this regard, interrupting survival signals mediated through the B-cell receptor appears to be one of the most promising approaches.²⁰ Multiple groups have now demonstrated single-agent

activity with a variety of compounds that interrupt B-cell receptor signaling pathway including SYK inhibitors²¹, PI3 kinase inhibitors, mTOR inhibitors, and Bruton's tyrosine kinase inhibitors^{22, 23}. Notably, these agents have generally been found to be well tolerated and to have the additional benefit of being orally administered. The activity of these targeted agents in relapsed/refractory CLL patients has created substantial interest in exploring how they may be incorporated into first-line therapy with the aim of improving efficacy and tolerability.

1.2 Ibrutinib (NSC 748645)

Ibrutinib is one of the most promising of these new compounds. Ibrutinib is an irreversible inhibitor of Bruton's tyrosine kinase (Btk), a member of the Tec family of tyrosine kinases and a protein which is over-expressed in patients with CLL. Btk is a critical protein involved in B cell development, differentiation, and signaling as well as B cell proliferation and survival.¹⁸ Inhibition of this kinase has been shown to cause modest apoptosis *in vitro*, and significantly inhibits B cell signaling both *in vitro* and *in vivo* (¹⁹ and unpublished data). The initial phase I studies examined dose escalation in various B cell malignancies. In this study, 15 patients with CLL were enrolled with objective response observed in 9/15 patients.(Fowler, ASH 2010) The drug was well tolerated at all dose levels examined, with only 5 out of 47 patients discontinuing therapy for toxicity. (Fowler, ASH 2010). A fluorescent-labeled probe was used to ensure that the doses brought forward occupied >90% of Btk,(Pollyea, ASCO 2009) and based on this study, a dose of 420 mg daily was established as a tolerable and effective dose. In an ongoing phase Ib/II study, this agent has shown extraordinary activity in 61 patients with relapsed or refractory CLL (O'Brien, ASH 2011). In patients with relapsed or refractory CLL and measurable adenopathy, the rate of lymph node shrinkage >50% is 89%. After a median follow-up of ~12 months, ORR is 68%.(O'Brien, ASH 2011). Transient lymphocytosis in this trial of Ibrutinib similar to that observed in clinical trials with the PI3 kinase delta inhibitor Cal-101 and is likely related to B-cell release from lymph node and spleen microenvironment due to disruption of homing signals or chemoattractants. Lymphocytosis with Ibrutinib agent has generally begun within the first 2 cycles, appears to resolve sooner than has been observed with Cal-101, and has resolved over time in virtually all patients. While this is currently under investigation, the magnitude and duration of lymphocytosis does not appear to be related to the depth of eventual response nor to response duration or toxicity. Response to Ibrutinib also occurs independently of high risk genomic features including IVGH mutational status and deletion(17p13.1). Studies are ongoing with this agent in both relapsed and previously untreated patients. The majority of patients in both groups remain on therapy and response over time has continued to improve as the majority of patients have had slow continued resolution of their lymphocytosis.

Thus far only 3 out of 83 patients have been removed from study for disease progression after 10-12 months follow-up. Oral Ibrutinib is well tolerated, with a very low rate of hematologic toxicity and few patients discontinuing therapy due to AE. The most common toxicities with Ibrutinib have been diarrhea, cough, fatigue, upper respiratory infection, rash, and bruising. Importantly, they do not overlap with the typical toxicities observed with CIT induction. The efficacy seen

thus far and tolerability of this agent administered continuously now to many patients for a year or more make it an ideal agent for further study.

The efficacy of Ibrutinib in combination with anti-CD20 monoclonal antibodies is also being explored in a multi-cohort phase 2 trial for patients with relapsed CLL and other B-cell malignancies at the Ohio State University. In the first cohort of 27 patients, Ibrutinib (430 mg) begins on day 1 and continues until disease progression with anti-CD20 monoclonal antibody treatment beginning month 2. All 27 patients completed the first month of therapy without a DLT. Of the 24 patients with CLL, a high rate of clinical activity has been observed and 23 patients remain on treatment (1 patient proceeded to non-ablative stem cell transplant). A second cohort of patients was accrued in whom the anti-CD20 monoclonal antibody treatment began on cycle 1 day 1 with Ibrutinib (420 mg) beginning cycle 1 day 2 (current accrual n=20). Nineteen patients completed 1 month of therapy and one patient suffered a subdural hematoma that was fatal. This patient was on warfarin and had other risk factors for developing this complication. Infusion toxicities with anti-CD20 monoclonal antibody on day 1 were manageable but in general were more severe than observed in the first cohort. A third cohort of patients where anti-CD20 monoclonal antibody is given for 8 weeks prior to beginning Ibrutinib is currently enrolling patients. Collectively, the Ohio State experience of giving Ibrutinib concurrent with anti-CD20 monoclonal antibody therapy suggests a run in with Ibrutinib for the first month followed by initiation of anti-CD20 monoclonal antibody beginning month two may be better tolerated. This schedule of administration will be pursued in this study.

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1.3 2015 Ibrutinib Safety Update

Pooled safety data are available for a total of 423 patients treated with various therapies in combination with ibrutinib across 4 studies conducted in B-cell malignancies, including 1 randomized-control study (Investigator's Brochure, 2015). 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). The most frequent TEAEs occurring in these patients are summarized below.

Ibrutinib Combination Therapy Studies (N=423)		
Most frequently reported TEAEs >20%	Most frequently reported Grade 3 or 4 TEAEs (>3%)	Most frequently reported Serious TEAEs (>2%)
Neutropenia	Neutropenia	Febrile neutropenia
Diarrhea	Thrombocytopenia	Pneumonia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Hypertension	

TEAE = treatment-emergent adverse event

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

1.3.1 Risks

Bleeding-related events

There have been reports of hemorrhagic events in patients treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Use of ibrutinib in patients requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Patients with congenital bleeding diathesis have not been studied.

Leukostasis

There were isolated cases of leukostasis reported in patients treated with ibrutinib. A high number of circulating lymphocytes ($>400000/\mu\text{L}$) may confer increased risk.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (i.e., $\geq 50\%$ increase from baseline and an absolute count $> 5000/\mu\text{L}$), often associated with reduction of lymphadenopathy, has been observed in most patients with CLL/SLL treated with ibrutinib. This effect has also been observed in some patients with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in patients with MCL and 18.7 weeks in patients with CLL/SLL.

A large increase in the number of circulating lymphocytes (e.g., $>400000/\mu\text{L}$) has been observed in some patients. Lymphocytosis was not observed in patients with WM treated with ibrutinib. Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in patients with CLL/SLL receiving ibrutinib in combination with chemoimmunotherapy.

Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in patients treated with ibrutinib, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation (Investigator's Brochure, 2015). For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in patients treated with ibrutinib (Investigator's Brochure, 2015).

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.

Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of patients with MCL and 35% of patients with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE) (Investigator's Brochure, 2015). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib.

Second Primary Malignancies

Other malignancies, most frequently skin cancers, have occurred in patients treated with ibrutinib.

Rash

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

Tumor Lysis Syndrome

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

1.4 Rationale

These early trials with Ibrutinib indicate that this agent is effective and well tolerated in patients with relapsed or refractory CLL and that combining Ibrutinib with anti-CD20 monoclonal antibodies is both well-tolerated and may improve efficacy. Ibrutinib has also been shown to antagonize microenvironment signals in CLL, which may make it particularly effective at clearing bone marrow disease which is a frequent site for residual disease at the completion of CIT²⁵. These characteristics, in combination with Ibrutinib's excellent tolerability profile and the fact it is an orally administered agent appear to make it ideally suited for testing as both induction therapy or as a consolidation strategy for eradicating residual disease after CIT induction.

The present trial is designed to compare targeted therapy using an oral, Bruton's tyrosine kinase inhibitor (Ibrutinib) to fludarabine-based induction (and reserve it as a salvage therapy) in younger patients (\leq age 70) with previously untreated CLL. The study employs a randomized phase III design.

1.5 Quality of Life

CLL has important impacts on patient QOL. Even though most patients with CLL are asymptomatic at the time of diagnosis and are observed for several years prior to starting treatment, the diagnosis has a substantial impact on emotional QOL even before symptoms develop.²⁶ Once patients progress to require treatment, they must deal not only with the effects of the disease on QOL but the effects of treatment.^{27, 28} Several studies suggest that QOL may decline during the active phase of fludarabine based treatment but that such therapy improves QOL over the long run by alleviating disease related symptoms.^{12, 28, 30} Not surprisingly, these studies also provide evidence that patients with a better response to treatment have greater improvements in QOL suggesting that disease control and improvements in QOL are linked.¹² Although it is possible that agents such as Ibrutinib may improve the QOL of CLL patients receiving first-line therapy relative to fludarabine-based therapy due to their apparent favorable toxicity profile, such an advantage may be short lived if they provide less effective disease control. In addition, although the toxicity profile of Ibrutinib appears favorable relative to fludarabine-based therapy, the need for chronic indefinite administration may result in chronic side effects that ultimately erode QOL over the long run compared to a more intense but limited treatment schedule. The present trial will assess QOL of CLL patients receiving Ibrutinib and fludarabine-based therapy to explore these aspects.

While the primary QOL objective is to assess the impact of therapy on QOL between two treatment arms, it is also important to assess the impact of treatment-related toxicity on QOL during treatment. Thus we will perform QOL assessments at baseline and at two time points during treatment (3 and six months after randomization). We will also evaluate the effects of these two treatment approaches over QOL over the longer term by assessing QOL at the time of the 12 month response evaluation and then every 6 months for 2 years. While those patients assigned to the FCR arm will be off active treatment at these points, patients assigned to the experimental Ibrutinib-based treatment arm will still be taking therapy. Thus the QOL of patients at these later time points may still differ between arms even though response rates may be equivalent. Moreover, as previously stated, improved QOL may be linked to improved disease control. This study provides us the opportunity to test this hypothesis by following patients longitudinally to see if improvements in QOL are sustained for a longer period of time in the disease control phase (up to 2 years after treatment) as well as to test for long-term differences in QOL between the two groups.

2. Objectives

2.1 Primary Objectives

- 2.1.1 The primary objective for the trial is to evaluate the ability of Ibrutinib - based induction therapy to prolong progression free survival (PFS) compared to standard FCR chemoimmunotherapy for younger patients with CLL.

2.2 Secondary Objectives

- 2.2.1 Evaluate overall survival (OS) of patients based on treatment arm.
- 2.2.2 Monitor and assess toxicity of treatment with Ibrutinib-based induction relative to standard FCR chemotherapy.
- 2.2.3 To compare quality of life (QOL) in CLL patients during the first 6 months of treatment among patients receiving Ibrutinib-based induction therapy relative to standard FCR chemoimmunotherapy.
- 2.2.4 To compare QOL over the long-term in CLL patients receiving continuous therapy using Ibrutinib to that of CLL patients who completed FCR therapy.
- 2.2.5 Determine the effect of pretreatment clinical and biological characteristics (e.g. disease stage, IGHV mutation status, FISH) on clinical outcomes (e.g. complete response, PFS) of the different arms
- 2.2.6 Determine if the minimal residual disease (MRD) status as assessed by flow cytometry at different time points during and after treatment is an effective surrogate marker for prolonged PFS and overall survival.
- 2.2.7 Compare the genetic abnormalities and dynamics of intra-clonal architecture of CLL patients before and after treatment with CIT and non-CIT approaches and explore relationships with treatment resistance.
- 2.2.8 Explore the effects of FCR and Ibrutinib-based therapy on T-cell immune function
- 2.2.9 Conduct confirmatory validation genotyping of single nucleotide polymorphisms (SNPs) associated with the efficacy and toxicity of fludarabine-based therapy as in a prior ECOG GWAS analysis in the E2997 trial.
- 2.2.10 Evaluate the ability of prognostic model that incorporates clinical and biologic characters to predict a response to therapy and clinical outcome (PFS, OS)
- 2.2.11 Evaluate signaling networks downstream of the B-cell receptor in patients receiving Ibrutinib-based therapy.
- 2.2.12 Collect relapse samples to study mechanisms of resistance to both FCR and Ibrutinib-based therapy.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

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3.1 Eligibility Criteria

_____ 3.1.1 Diagnosis of CLL according to the NCI/IWCLL criteria or SLL according to the WHO criteria.

This includes **previous** documentation of:

- Biopsy-proven small lymphocytic lymphoma
- OR
- Diagnosis of CLL according to the NCI/IWCLL criteria as evidenced by all of the following:
 - Peripheral blood lymphocyte count of greater than $5 \times 10^9/L$
 - Immunophenotype consistent with CLL defined as:
 - The predominant population of lymphocytes share both B-cell antigens [CD19, CD20 (typically dim expression), or CD23] as well as CD5 in the absence of other pan-T-cell markers (CD3, CD2, etc).
 - Clonality as evidenced by κ or λ light chain restriction (typically dim immunoglobulin expression)
- Negative FISH analysis for t(11;14)(IgH/CCND1) on peripheral blood or tissue biopsy (e.g. marrow aspirate) or negative immunohistochemical stains for cyclin D1 staining on involved tissue biopsy (e.g. marrow aspirate or lymph node biopsy).

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_____ 3.1.2 No prior chemotherapy, BTK inhibitor therapy, or monoclonal antibody therapy for treatment of CLL or SLL

- _____ 3.1.3 Has met **at least one** of the following indications for treatment:
- Evidence of progressive marrow failure as manifested by the development of worsening anemia (Hb < 11 g/dl) and/or thrombocytopenia (Platelets < 100 x 10⁹/L)
 - Symptomatic or progressive lymphadenopathy, splenomegaly, or hepatomegaly.
 - One or more of the following disease-related symptoms:
 - Weight loss ≥ 10% within the previous 6 months
 - Grade 2 or 3 fatigue attributed to CLL
 - Fevers >100.5°F for 2 weeks without evidence of infection
 - Clinically significant night sweats without evidence of infection
 - Progressive lymphocytosis (not due to the effects of corticosteroids) with an increase of >50% over a two-month period or an anticipated doubling time of less than six months.
- _____ 3.1.4 Age ≥ 18 years and ≤ 70
- _____ 3.1.5 ECOG performance status between 0-2.
- _____ 3.1.6 Life expectancy of ≥ 12 months
- _____ 3.1.7 Ability to tolerate FCR based therapy
- _____ 3.1.8 No deletion of 17p13 on cytogenetic analysis by FISH
- _____ 3.1.9 The following laboratory values obtained ≤ 14 days prior to registration:
- _____ Glomerular filtration rate (GFR) > 40 mL/minute as calculated by the Cockcroft-Gault Formula:
- $$\text{CrCl (ml/min)} = \frac{(140 - \text{age in years}) \times \text{actual wt (in kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times 0.85 \text{ (for female pts)}$$
- _____ Total bilirubin ≤ 2.5 x ULN unless due to Gilbert's disease. For those with a total bilirubin > 2.5 x ULN, a direct bilirubin should be performed and must be < 1.5 mg/dL for Gilbert's to be diagnosed.
- _____ SGOT (AST)/SGPT (ALT) ≤ 3.0 x the institutional ULN
- _____ PT/INR < 1.5 ULN and PTT (aPTT) < 1.5 X ULN
- NOTE:** If value is higher due to hepatic involvement by CLL, patient is eligible.
- _____ 3.1.10 No active hemolytic anemia requiring immunosuppressive therapy or other pharmacologic treatment. Patients who have a positive Coombs test but no evidence of hemolysis are NOT excluded from participation.
- _____ 3.1.11 No current use of corticosteroids. EXCEPTION: Low doses of steroids (< 10 mg of prednisone or equivalent dose of other steroid) used for treatment of non-hematologic medical condition (e.g. chronic adrenal insufficiency) is permitted.

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- _____ 3.1.12 No previous use of corticosteroids for autoimmune complications that have developed since the initial diagnosis of CLL. Prior use of corticosteroids for reasons other than treatment of autoimmune complications is allowed.
- _____ 3.1.13 No other active primary malignancy (other than non-melanomatous skin cancer or carcinoma in situ of the cervix) requiring treatment or limiting expected survival to ≤ 2 years.
- NOTE:** If there is a history of prior malignancy, they must not be receiving other specific treatment (other than hormonal therapy for their cancer).
- _____ 3.1.14 Able to adhere to the study visit schedule and other protocol requirements.
- _____ 3.1.15 No major surgery within 4 weeks (28 days) of first dose of study drug or minor surgery within 3 days of first dose of study drug.
- _____ 3.1.16 No radiation therapy ≤ 4 weeks prior to registration
- _____ 3.1.17 Patients with HIV infection may be eligible provided they meet the following criteria:
- CD4-positive cell count \geq lower limit of institutional normal
 - HIV viral load $< 10,000$ copies HIV RNA/mL (if not on anti-HIV therapy) OR < 50 copies HIV RNA/mL (if on anti-HIV therapy)
 - No evidence of hepatitis B or C infection
 - No evidence of resistant strains of HIV
 - No history of AIDS-defining condition
- _____ 3.1.18 Patients must not have any of the following conditions:
- Congestive heart failure or New York Heart Association Functional Classification III or IV congestive heart failure
 - History of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to registration.
 - Recent infections requiring systemic treatment; need to have completed anti-biotic therapy >14 days before the first dose of study drug.
 - Cerebral vascular accident or intracranial bleed within the last 6 months
 - Infection with known chronic, active hepatitis C.
 - Serologic status reflecting active hepatitis B or C infection. Patients that are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) prior to enrollment (PCR positive patients will be excluded).
- _____ 3.1.19 Patients are not eligible if they require treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see [Appendix VIII](#)). For additional information regarding use of moderate CYP3A4/5 inhibitors see Section [8.1.12](#).
-

-
- _____ 3.1.20 Patients may not be on any other investigational agents
- _____ 3.1.21 Patients may not have received warfarin or another vitamin K antagonist in the preceding 30 days.
- _____ 3.1.22 Women must not be pregnant or breast-feeding since this study involves an investigational agent whose genotoxic, mutagenic, and teratogenic effects on the developing fetus and newborn are unknown.
- Female patients of childbearing potential must have a negative serum pregnancy test within 2 weeks prior to registration to rule out pregnancy. Female patients who are of non-reproductive potential are those who are post-menopausal by history (i.e. no menses for ≥ 1 year); OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy)
- Female? _____ (Yes or No)
- Date of blood test or urine study: _____
- _____ 3.1.23 Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for 90 days after the last dose of study drug.
- _____ 3.1.24 Patient must be able to swallow capsules and not have the following conditions:
- disease significantly affecting gastrointestinal function
 - resection of the stomach or small bowel
 - symptomatic inflammatory bowel disease
 - ulcerative colitis
 - partial or complete bowel obstruction
- _____ 3.1.25 Patient must not be on any other systemic immunosuppressant therapy other than corticosteroids within 28 days of the first dose of study drug.
- _____ 3.1.26 Patient must not be vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
- _____ 3.1.27 Patient must not have any known bleeding disorders (e.g., von Willebrand's disease) or hemophilia.

_____ 3.1.28 Patient must not have currently active, clinically significant hepatic impairment (\geq moderate hepatic impairment according to the NCI/Child Pugh classification [[Appendix XII](#)])

Physician Signature

Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation

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4. Registration Procedures

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed **Statement of Investigator Form** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed **Supplemental Investigator Data Form** (IDF)
- a completed **Financial Disclosure Form** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the **CTEP Investigator Registration Help Desk** by email at pmbregpend@ctep.nci.nih.gov.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the **CTEP Associate Registration Help Desk** by email at ctepreghelp@ctep.nci.nih.gov.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials

at <https://www.ctsu.org>. For sites under the CIRB initiative, IRB data will automatically load to RSS.

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Sites participating on the NCI CIRB initiative that are approved by the CIRB for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. However, sites must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB (via IRBManager) to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office for compliance in the RSS. The Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in a given study so that the study approval can be applied to those institutions. Other site registration requirements (e.g., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

Downloading Site Registration Documents

Site registration forms may be downloaded from the **E1912** protocol page located on the CTSU members' website.

- Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E1912**
- Click on the Site Registration Documents link

Requirements for E1912 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Submitting Regulatory Documents

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Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103

PHONE: 1-866-651-2878

FAX: (215) 569-0206

EMAIL: CTSURegulatory@ctsu.cocccg.org (for regulatory document submission only)

Required Protocol Specific Regulatory Documents

1. **CTSU Regulatory Transmittal Form.**
2. **Copy of IRB Informed Consent Document.**

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3.
 - A. **CTSU IRB Certification Form.**
Or
 - B. **Signed HHS OMB No. 0990-0263 (replaces Form 310).**
Or
 - C. **IRB Approval Letter**

NOTE: The above submissions must include the following details:

- **Indicate all sites approved for the protocol under an assurance number.**
- **OHRP assurance number of reviewing IRB**
- **Full protocol title and number**
- **Version Date**
- **Type of review (full board vs. expedited)**
- **Date of review.**
- **Signature of IRB official**

Checking Your Site's Registration Status

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Patient Enrollment

Patients must not start protocol treatment prior to registration.

Treatment should start within 14 working days after registration.

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < <https://eapps-ctep.nci.nih.gov/iam/index.jsp> >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the database. OPEN can be accessed at <https://open.ctsu.org> or from the OPEN tab on the CTSU members' side of the website at <https://www.ctsu.org>.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria has been met within the protocol stated timeframes. All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at <https://www.ctsu.org> or at <https://open.ctsu.org>. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

The following information will be requested

4.1 Protocol Number

4.2 Investigator Identification

4.2.1 Institution and affiliate name (Institution CTEP ID)

4.2.2 Investigator's name (NCI number)

4.2.3 Cooperative Group Credit

4.2.4 Credit Investigator

4.2.5 Protocol specific contact information

4.3 Patient Identification

4.3.1 Patient's initials (first and last)

4.3.2 Patient's Hospital ID and/or Social Security number

4.3.3 Patient demographics

4.3.3.1 Gender

4.3.3.2 Birth date

4.3.3.3 Race

4.3.3.4 Ethnicity

4.3.3.5 Nine-digit ZIP code

4.3.3.6 Method of payment

4.3.3.7 Country of residence

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section [3](#).

4.5 Stratification Factors:

4.5.1 Age: < 60 years vs. ≥ 60 years

4.5.2 PS 0,1 vs 2

4.5.3 Disease stage: 3/4 vs. 1/2

4.5.4 Baseline cytogenetic abnormalities on FISH: deletion 11q22.3(ATM) vs. other

4.6 Additional Requirements

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4.6.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office -- Boston.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office. However the ECOG-ACRIN Leukemia Translational Research Laboratory (LTRL) requires institutions to submit a copy of the E1912 consent and a copy of the HIPAA authorization form.

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4.6.2 Bone marrow sections/slides and smears must be submitted for central review as outlined in Section [10](#).

4.6.3 Peripheral blood and buccal cells should be submitted for correlative studies and/or banking as outlined in Section [10](#), per patient consent.

NOTE: ECOG-ACRIN requires that biological samples submitted from patients participating in E1912 be entered and tracked via the on-line ECOG-ACRIN Sample Tracking System (STS) (see Section [10.4](#)).

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NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG-ACRIN Operations Office – Boston regarding logistics for submission of fresh samples.

4.6.4 Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata the site user must have an active CTEP IAM account (check at <<https://eapps-ctep.nci.nih.gov/iam>>) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (<https://login.imedidata.com/selectlogin>) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU members’ website, Rave tab under the Rave resource materials

(Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at <http://www.ctsu.org/RAVE/> or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

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ECOG-ACRIN has contracted with Alpha Oncology, a contract research organization (CRO) to conduct on-site and remote monitoring activities. The goal of these monitoring activities is to provide source document verification (SDV). Alpha Oncology will be in contact with sites as patients reach the pre-defined milestones for initiation of monitoring activities.

Alpha Oncology will also be conducting data sweeps. The goal of these data sweeps is to assist institutions with timely data entry and query resolution. Alpha Oncology will utilize phone requests and email notifications to request entry of outstanding data and/or completion of open queries. The objective of these sweeps is to collect data; they are not designed as an audit, nor are they intended to generate corrections to previously submitted data.

Alpha Oncology will report only to ECOG-ACRIN per contract and information obtained from monitoring will be shared only with ECOG-ACRIN.

4.7 Investigational Brochure

Ibrutinib is an INVESTIGATIONAL AGENT (IND# 117241). A copy of the Investigator's Brochure (IB) can be obtained by calling the Pharmaceutical Management Branch at the NCI (240-276-6575) or via email request to ibcoordinator@mail.nih.gov.

NOTE: Please have your investigator's NCI # handy. The IB provides relevant and current scientific information about the investigational product. Please submit the IB to your IRB/EC according to GCP regulations. The IB and any correspondence to the IRB should be kept in the study files of E1912.

4.8 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E1912 Forms Completion Guidelines. Document the reason for not starting protocol treatment on the Off Treatment form. Also report the date and type of the first non-protocol treatment that the patient receives.

5. Treatment Plan

5.1 Administration Schedule

All questions regarding treatment and dose modifications should be directed to the ECOG-ACRIN Study Chair.

All drugs that will be administered according to weight should be dosed according to actual body weight. There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by (1) the patient's BSA as calculated from actual weight or (2) actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese patients on this protocol.

Intravenous medications in both study arms may be administered via the following methods: peripheral IV, Port-a-cath, central line, PIC, or Hickman.

NOTE: BSA will be calculated prior to each cycle based on body weight at the start of that cycle. Accordingly, the dose of drugs based on BSA (e.g. fludarabine, cyclophosphamide, rituximab) may vary slightly cycle by cycle due to fluctuations in body weight. Changes to doses cycle by cycle are allowed but not required unless calculated dose changes by greater than 10%.

NOTE: Doses can be rounded using the following guidelines:

Rituximab 50 mg/m² round to nearest 5 mg

Rituximab 325 mg/m² round to nearest 10 mg

Rituximab 500 mg/m² round to nearest 10 mg

Fludarabine round to nearest 1 mg

Cyclophosphamide round to nearest 10 mg

5.1.1 ARM A: Ibrutinib with Rituximab

Therapy will consist of daily oral Ibrutinib in combination with rituximab. For the first month of therapy patients will receive Ibrutinib alone. Beginning with the second cycle, patients will receive rituximab. Since the rituximab begins in cycle 2 rather than cycle 1, patients will receive rituximab during cycles 2-7 so that they receive an identical cumulative dose of rituximab to arm B. After completion of cycle 7, patients will continue on daily oral Ibrutinib until disease progression. Patients will be assessed with physical examination, CBC, and chemistries prior to cycle 1-7 as per Section [7.1](#). Beginning day 1 of cycle 7, patients will be seen every 90 days (+/-7 days).

NOTE: Ibrutinib should be taken with 8 ounces (approximately 240 ml) of water. The capsules are to be swallowed intact, not less than 30 minutes before or 2 hours after a meal. Patients should avoid consuming food and beverages

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containing grapefruit juice or Seville oranges for the duration of the study due to CYP3A4/5 inhibition.

NOTE: Doses are to be taken at about the same time each day. If an ibrutinib dose is missed, it should be made up as soon as possible on the same day with a return to the normal schedule the following day.

NOTE: Patients require antibiotic prophylaxis for PCP/PJP and zoster as delineated in [5.5.2](#).

5.1.1.1 Drugs

Cycle 1:

- Ibrutinib 420 mg orally once per day for 28 days (+/- 4 days)
- Patients will be seen every 28 days (+/- 4 days)

NOTE: Patients with a baseline platelet counts below $20 \times 10^9/L$ should receive platelet transfusion prior to starting Ibrutinib therapy. As noted in Section [7.0](#), patients whose baseline platelet count is below $20 \times 10^9/L$ should have repeat CBC on day 3.

Cycles 2-7:

- Ibrutinib 420 mg orally once per day for 28 days (+/- 4 days)
- Rituximab, 50 mg/m² IV on day 1 of Cycle 2, and 325 mg/m² on day 2 of Cycle 2, then 500 mg/m² on day 1 of Cycles 3-7.

NOTE: Patients with a baseline platelet counts below $20 \times 10^9/L$ should receive platelet transfusion prior cycle 2, day 1 rituximab therapy. As treatment with anti-CD20 monoclonal antibodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts $< 50 \times 10^9/L$, prior to receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.

- Repeat cycles every 28 days (+/- 4 days) for a total of 6 cycles
- Since monthly visits are required during cycles 1-6, a 1 month supply of drug should be dispensed to patient during these cycles. Since 3 month visits are required after cycle 6, a 3 month supply of drug may be dispensed for cycle 7 and beyond.

After cycle 7

- Ibrutinib 420 mg orally once per day continuously until disease progression.

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-
- During this phase patients will be seen every 90 days (+/-7 days)
- Rev. 1/16 **NOTE:** Please see Section [5.5.8](#) for dose modifications to ibrutinib if patients require treatment with a CYP3A inhibitor/inducer or any medication known to cause QT prolongation.
- Rev. 7/14 5.1.1.2 Unless otherwise indicated, premedication prior to all doses of rituximab (Cycles 2-7) will include the following:
- Hydrocortisone 100 mg IV (or equivalent dose of other corticosteroid) should be administered before the first and second doses of rituximab during Cycle 2 of therapy. Thereafter, it should only be administered if patients have infusion reactions or nausea that is not controlled by alternative anti-emetics.
- Rev. 8/15 • Diphenhydramine 50 mg IV or PO (or alternative anti-histamine) and acetaminophen 650 mg PO should be administered 30 minutes prior to rituximab to reduce infusion reactions. Patients with allergic reactions to diphenhydramine and other anti-histamines may have anti-histamines held at the discretion of the treating physician.
- Rev. 7/14 5.1.1.3 The following premedication will be administered prior to Cycles 1 and 2:
- All patients will be given PO allopurinol 300 mg/day from day 1 to day 14 (a total of 14 days) of Cycles 1 and 2 unless they are allergic. Treatment with allopurinol may continue beyond 14 days during Cycles 1 and 2 at the discretion of the treating physician. Use of allopurinol with subsequent cycles will be at the discretion of the treating physician.
 - Use of antiemetic therapy will be left to the discretion of the treating physician
- 5.1.1.4 Ibrutinib 420 mg orally once per day on days 1-28 days of cycles 1-7. After the end of cycle 7, patients will remain on Ibrutinib 420 mg orally once per day until disease progression. *During this phase patients will be seen every 90 days (+/-7 days)*
- 5.1.1.5 Rituximab administration:
- On day 1 Cycle 2:** rituximab 50 mg/m² mg will be administered IV over a period of 4 hours. To determine the hourly rate of infusion, divide the total volume of rituximab solution by 4 and administer at this rate, without escalation, for 4 hours. Shortness of breath, rigors and other infusion-related toxicities have been noted more frequently during the first infusion and in patients with high leukocyte counts. Vital signs are recommended to be measured every 15 minutes for the first 2 hours with the first dose of rituximab.

If patient is unable to complete rituximab on day 1 of cycle 2, the residual rituximab dose should be administered on day 2.

On day 2 of Cycle 2: rituximab 325 mg/m² will be administered IV. Rituximab can usually be initiated at 50 mg/hr. If hypersensitivity or infusion related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. Close observation for infusion-related toxicities should occur throughout the infusion, particularly with each dose escalation.

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On day 1 of cycles 3-7: rituximab 500 mg/m² will be administered IV. If the patient tolerated the most recent infusion, rituximab can usually be initiated at 100 mg/hr. If hypersensitivity or infusion related events do not occur, escalate the infusion rate in 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. Close observation for infusion-related toxicities should occur throughout the infusion, particularly with each dose escalation. If the patient did not tolerate the most recent infusion, initiate rituximab at 50 mg/hr (or lower rate if necessary) and follow the Cycle 2 day 2 infusion schedule. If a reaction occurs, slow or stop the infusion. If the reaction abates, restart infusion at 50% of the previous rate. Close observation for infusion-related toxicities should occur throughout the infusion, particularly with each dose escalation. If patient is unable to complete rituximab on day 1 of cycles 3-7, the residual rituximab dose should be administered on day 2 of that cycle.

Rituximab Infusion reactions:

- Shortness of breath, rigors and other infusion-related toxicities have been noted more frequently in patients with high leukocyte counts and during the first several treatments. Close observation for these potential toxicities should occur. The treatment area should be sufficiently prepared to allow easy access to supportive care medications and measures, such as meperidine for IV push, oxygen supplementation and nebulized albuterol, warm blankets, IV fluid for bolus, and access to crash cart.
- If infusion reactions occur, infusions should be stopped until infusion-related symptoms resolve, and then resumed at a 50% slower rate. Contact the ECOG-ACRIN Study Chair or ECOG-ACRIN Committee chair with any questions.
- If transient bronchospasm occurs, rituximab administration should be interrupted. If these symptoms persist, albuterol (or other B₂ agonist) by

inhalation and additional hydrocortisone should be administered at the discretion of the treating physician.

- In patients with high leukocyte counts, close observation for potential toxicities should occur. If marked reduction in circulating lymphocytes is noted, close attention to the possibility of acute tumor lysis syndrome should occur.

5.1.2 As treatment with anti-CD20 monoclonal anti-bodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts $< 50 \times 10^9/L$ prior to receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary. Criteria for converting patients who do not respond to Ibrutinib therapy

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On day 1 of cycle 5 (e.g. after completing cycle 4), patients will be assessed with physical examination and CBC as per Section 7.1. Patients with progressive disease or those who have not experienced at least a $\geq 50\%$ reduction in lymphadenopathy will be considered to have failed Ibrutinib based therapy. These patients will be considered a treatment failure and will discontinue Ibrutinib-based therapy. If deemed appropriate by their treating physician, patients may receive salvage therapy (off protocol) with FCR for 6 cycles using the schedule outlined for Arm B.

NOTE: It should be noted that it is common for CLL patients treated with Ibrutinib to experience a transient increase in lymphocytosis due to redistribution of lymphocytes from the lymph nodes and spleen to the peripheral blood circulation. This lymphocytosis is NOT a marker of disease progression or Richter's transformation and typically resolves over several months. For this reason, no patient on Ibrutinib will be considered to have disease progression based on an increased absolute lymphocyte count that occurs during the first several months of Ibrutinib based treatment. See protocol Section 5.1.2. Questions regarding an increase in the absolute lymphocyte count after initiation of Ibrutinib-based therapy should be discussed with the study PI.

5.1.3 ARM B: FCR for 6 cycles

Therapy will consist of 6 28-day cycles of fludarabine, cyclophosphamide, and rituximab. The sequence of drug administration is as follows: (1) rituximab, (2) fludarabine, (3) CTX. Patients will be assessed with physical examination, CBC, and chemistries prior to cycle 1-6 as per Section 7.1. Patients will also be evaluated at the end of cycle 6, 90 days (+/-7 days) after the end of cycle 6 and then 12 months post registration as outlined in Section 7.1.

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NOTE: Patients require antibiotic prophylaxis for PCP/PJP and zoster as delineated in 5.5.2.

5.1.3.1 Drugs

Cycles 1 – 6:

- Rituximab, 50 mg/m² IV on day 1 and 325 mg/m² on day 2 of Cycle 1 and 500 mg/m² on day 1 of Cycles 2-6.
- Fludarabine 25 mg/m², IV, days 1, 2, 3
- Cyclophosphamide 250 mg/m², IV, days 1, 2, 3
- Repeat cycles every 28 days (+/- 4 days) for a total of 6 cycles.

NOTE: Patients with a pre-treatment platelet counts below 20x10⁹/L should receive platelet transfusion prior cycle 1, day 1 rituximab therapy. As noted in Section 7.0, patients whose pre-treatment platelet count is below 20x10⁹/L should have repeat CBC on day 3.

As treatment with anti-CD20 monoclonal antibodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts < 50 x10⁹/L prior to receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.

5.1.3.2 Unless otherwise indicated, premedication prior to all doses of rituximab (Cycles 1-6) will include the following:

- Hydrocortisone 100 mg IV (or equivalent dose of other corticosteroid) should be administered before the first and second doses of rituximab during Cycle 1 of therapy. Thereafter, it should only be administered if patients have infusion reactions or nausea that is not controlled by alternative anti-emetics.
- Diphenhydramine 50 mg IV or PO and acetaminophen 650 mg PO should be administered 30 minutes prior to rituximab to reduce infusion reactions. Patients with allergic reactions to diphenhydramine may receive an alternative anti-histamine or have anti-histamines held at the discretion of the treating physician.

5.1.3.3 The following premedication will be administered prior to Cycles 1-6:

- All patients will be given PO allopurinol 300 mg/day from day 1 to day 14 (a total of 14 days) of Cycle 1 unless they are allergic. Treatment with allopurinol may continue beyond 14 days at the discretion of the treating physician. Use of allopurinol with subsequent cycles will be at the discretion of the treating physician.
- Antiemetic medications such as Kytril 1 mg PO (or substitute) should be given thirty minutes to 1 hour

prior to chemotherapy (fludarabine and/or cyclophosphamide). Additional prophylactic antiemetic therapy will be left to the discretion of the treating physician

- All patients should be well hydrated before each cycle of therapy. Patients should be encouraged to drink fluids the night before treatment and will receive approximately 500 to 1000 mL of IV hydration over 1 hour prior to chemotherapy on days they receive fludarabine and cyclophosphamide.
- On Day 2 of Cycle 1 only, CBC with differential, Ca⁺⁺, PO₄, LDH, uric acid, electrolytes, and creatinine are required to assess for tumor lysis syndrome prior to the second fludarabine dose (see Section [7.1](#)).

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5.1.3.4 Rituximab administration:

On day 1 Cycle 1: rituximab 50 mg/m² mg will be administered IV over a period of 4 hours. To determine the hourly rate of infusion, divide the total volume of rituximab solution by 4 and administer at this rate, without escalation, for 4 hours. Shortness of breath, rigors and other infusion-related toxicities have been noted more frequently during the first infusion and in patients with high leukocyte counts. Vital signs are recommended to be measured every 15 minutes for the first 2 hours with the first dose of rituximab. If patient is unable to complete cycle 1, day 1 rituximab dose, the residual rituximab should be added to cycle 1, day 2 dose.

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On day 2 of Cycle 1: rituximab 325 mg/m² will be administered IV. Rituximab can usually be initiated at 50 mg/hr. If hypersensitivity or infusion related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. Close observation for infusion-related toxicities should occur throughout the infusion, particularly with each dose escalation. If patient is unable to complete cycle 1, day 2 rituximab dose, the residual rituximab may be administered on cycle 1, day 3.

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On day 1 of cycles 2-6: rituximab 500 mg/m² will be administered IV. If the patient tolerated the most recent infusion, rituximab can usually be initiated at 100 mg/hr. If hypersensitivity or infusion related events do not occur, escalate the infusion rate in 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. Close observation for infusion-related toxicities should occur throughout the infusion, particularly with each dose escalation. If the patient did not tolerate the most recent infusion, initiate rituximab at 50 mg/hr (or lower rate if necessary) and follow the Cycle 1 day 2 infusion schedule. If a reaction occurs, slow or stop the infusion. If the reaction abates,

restart infusion at 50% of the previous rate. Close observation for infusion-related toxicities should occur throughout the infusion, particularly with each dose escalation. If patient is unable to complete rituximab on day 1 of cycles 2-6, the residual rituximab dose should be administered on day 2 of that cycle.

Rituximab Infusion reactions:

- Shortness of breath, rigors and other infusion-related toxicities have been noted more frequently in patients with high leukocyte counts and during the first several treatments. Close observation for these potential toxicities should occur. The treatment area should be sufficiently prepared to allow easy access to supportive care medications and measures, such as meperidine for IV push, oxygen supplementation and nebulized albuterol, warm blankets, IV fluid for bolus, and access to crash cart.
- If infusion reactions occur, infusions should be stopped until infusion-related symptoms resolve, and then resumed at a 50% slower rate. Contact the ECOG-ACRIN Study Chair or ECOG-ACRIN Committee chair with any questions.
- If transient bronchospasm occurs, rituximab administration should be interrupted. If these symptoms persist, administration of albuterol (or other B2 agonist) by inhalation and additional hydrocortisone should be administered at the discretion of the treating physician.
- In patients with high leukocyte counts, close observation for potential toxicities should occur. If marked reduction in circulating lymphocytes is noted, close attention to the possibility of acute tumor lysis syndrome should occur.
- As treatment with anti-CD20 monoclonal anti-bodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts $< 50 \times 10^9/L$ prior to receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.

5.1.3.5 Fludarabine monophosphate 25 mg/m²/day IV over 30 minutes on days 1-3 of Cycles 1-6.

(In Canada, it is permissible to substitute fludarabine monophosphate 40 mg/m²/day orally on days 1-6 of each cycle.

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5.1.3.6 Cyclophosphamide 250 mg/m²/day IV over 30 minutes on days 1-3 of Cycles 1-6.

Criteria for converting patients who do not respond to FCR induction to Ibrutinib

Patients will be assessed with physical examination and CBC prior to each cycle as per Section [7.1](#). Patients with progressive disease (see Section [6.1.3](#)) will be considered to have failed FCR-based therapy. These patients will be considered a treatment failure for the primary analysis and, salvage therapy can be initiated with the regimen deemed most appropriate by their treating physician.

Patients will be seen every 28 days (+/- 7 days) for the first 6 months of treatment with Ibrutinib at which point the frequency of follow-up can be spaced to every 90 days (+/- 7 days) at the discretion of the treating physician

5.1.3.7 Patients who relapse after FCR

After they complete induction therapy, patients responding to FCR will be followed according as per Section [7.1](#). The criteria for progressive disease during follow-up are defined in Section [6.1.3](#). Many patients with progressive disease are asymptomatic and can be observed until they experience:

- Evidence of progressive marrow failure as manifested by the development of worsening anemia (Hgb < 11 g/dl) and/or thrombocytopenia (Platelets < 100 x 10⁹/L)
- Symptomatic or progressive lymphadenopathy, splenomegaly, or hepatomegaly.
- One or more of the following disease-related symptoms:
 - Weight loss > 10% within the previous 6 months
 - Grade 2 or 3 fatigue attributed to CLL
 - Fevers > 100.5°F for 2 weeks without evidence of infection
 - Clinically significant night sweats without evidence of infection

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Patients fulfilling the criteria for progressive disease (Section [6.1.3](#)) and in need of salvage therapy as determined by the treating physician may be treated with the salvage therapy regimen deemed most appropriate by their treating physician.

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5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the

patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting:** Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave. On this protocol, all adverse events, of any grade, regardless of attribution to study treatment, will be recorded on the *E1912 Adverse Event Form*.
- **Expedited reporting:** In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

NOTE: Effective April 1, 2018 expedited adverse event reporting done via CTEP-AERS will use CTCAE version 5.0 terminology and grading. Routine adverse event reporting and dose modifications guidelines will continue to be based on CTCAE version 4.0 terminology and grading.

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5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is clearly NOT related to treatment
Unlikely	The AE is doubtfully related to treatment
Possible	The AE may be related to treatment
Probable	The AE is likely related to treatment
Definite	The AE is clearly related to treatment

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.

- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
 - Death
 - A life-threatening adverse event
 - Inpatient hospitalization or prolongation of existing hospitalization (for \geq 24 hours).
 - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
 - A congenital anomaly/birth defect.
 - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should **ONLY be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.**

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5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at <http://ctep.cancer.gov>. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at <http://ctep.cancer.gov>.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610) for Arms A and B
- the CTEP/NCI (301-897-7497) for Arm A and Arm B

An electronic report **MUST** be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation (for Arms A and B) must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the

CTEP/NCI (301- 230-0159) for Arm A and) for Arm B in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

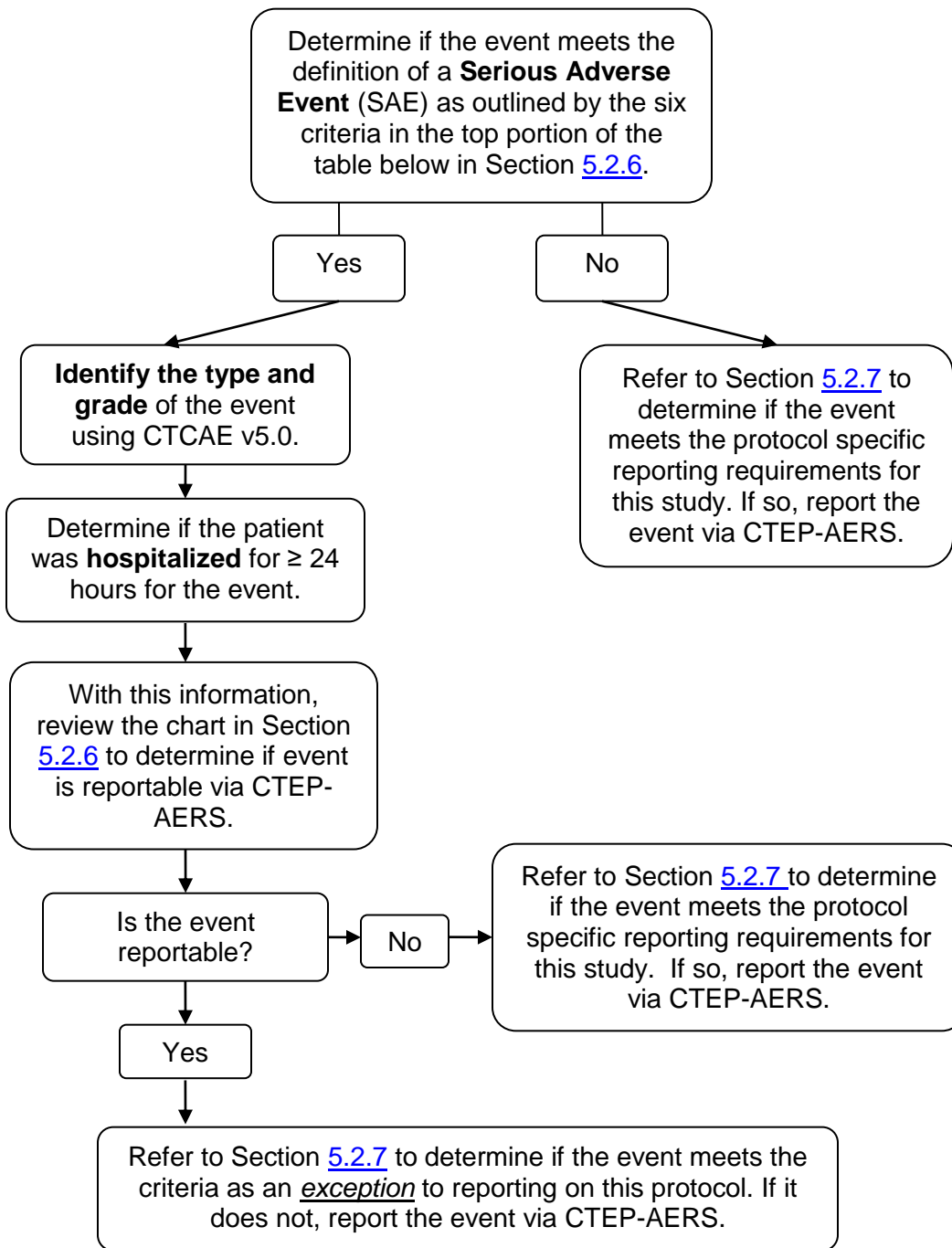
- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. \geq 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol E1912 and outline the specific expedited adverse event reporting requirements for study E1912.

Rev. Add8

5.2.5 Steps to determine if an adverse event is to be reported in an expedited manner – Arm A

5.2.5.1 Guidelines for adverse events **OCcurring WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.2.5.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section [5.2.6](#), AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or considered important medical event
- Grade 3 adverse events only if meets serious criteria

5.2.6 Expedited Reporting Requirements for Arm A on protocol E1912

Investigational Agents: Ibrutinib

Commercial Agents: Rituximab

Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of the Investigational Agent/Intervention.¹

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

<p>FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)</p> <p>NOTE: Investigators MUST immediately report to the sponsor (NCI) ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)</p> <p>An adverse event is considered serious if it results in ANY of the following outcomes:</p> <ol style="list-style-type: none"> 1. Death 2. A life-threatening adverse event 3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5. A congenital anomaly/birth defect. 6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). 				
<p>ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.</p>				
Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days		
<p>NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.</p> <p>Expedited AE reporting timelines are defined as:</p> <ul style="list-style-type: none"> • “24-Hour; 5 Calendar Days” – The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report. • “10 Calendar Days” – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE. 				
<p>¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:</p> <p>Expedited 24-hour notification followed by complete report within 5 calendar days for:</p> <ul style="list-style-type: none"> • All Grade 4, and Grade 5 AEs <p>Expedited 10 calendar day reports for:</p> <ul style="list-style-type: none"> • Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization • Grade 3 adverse events 				

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5.2.7

Additional instructions, requirements and exceptions for protocol
E1912 – Arm A

Rev. 1/16

Additional Instructions:

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please the AEMD Help Desk at aemd@tech-res.com or 301-897-7497.. This will need to be discussed on a case by case basis.

E1912 additional expedited reporting requirements:**Pregnancy**

- Although not an adverse event in and of itself, pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease status) occurring in a female patient or a female partner of a male patient while the subject is on lbrutinib, or within 90 days of the subjects last does of lbrutinib, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge.

Please refer to [Appendix IX](#) for detailed instructions on how to report the occurrence of a pregnancy, the outcome of all pregnancies, as well as a link to the NCI's Pregnancy Information Form that must be completed.

Other Adverse Events:

- Any \geq grade 3 occurrence of the following events must be reported via CTEP-AERS regardless whether or not the patient was hospitalized or if it appears in the SPEER. Report the event within the timeframes outlined in the chart in Section [5.2.6](#).
 - Diarrhea/Nausea/Vomiting
 - Fatigue
 - Febrile Neutropenia
 - Fever
 - Headache
 - Hematuria
 - Infusion related reaction
 - Lower or upper gastrointestinal hemorrhage
 - Lung infection
 - Myalgia
 - Rash maculo-papular
 - Sepsis
 - Upper respiratory infection

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- 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.

E1912 specific expedited reporting exceptions:

If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should **ONLY** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

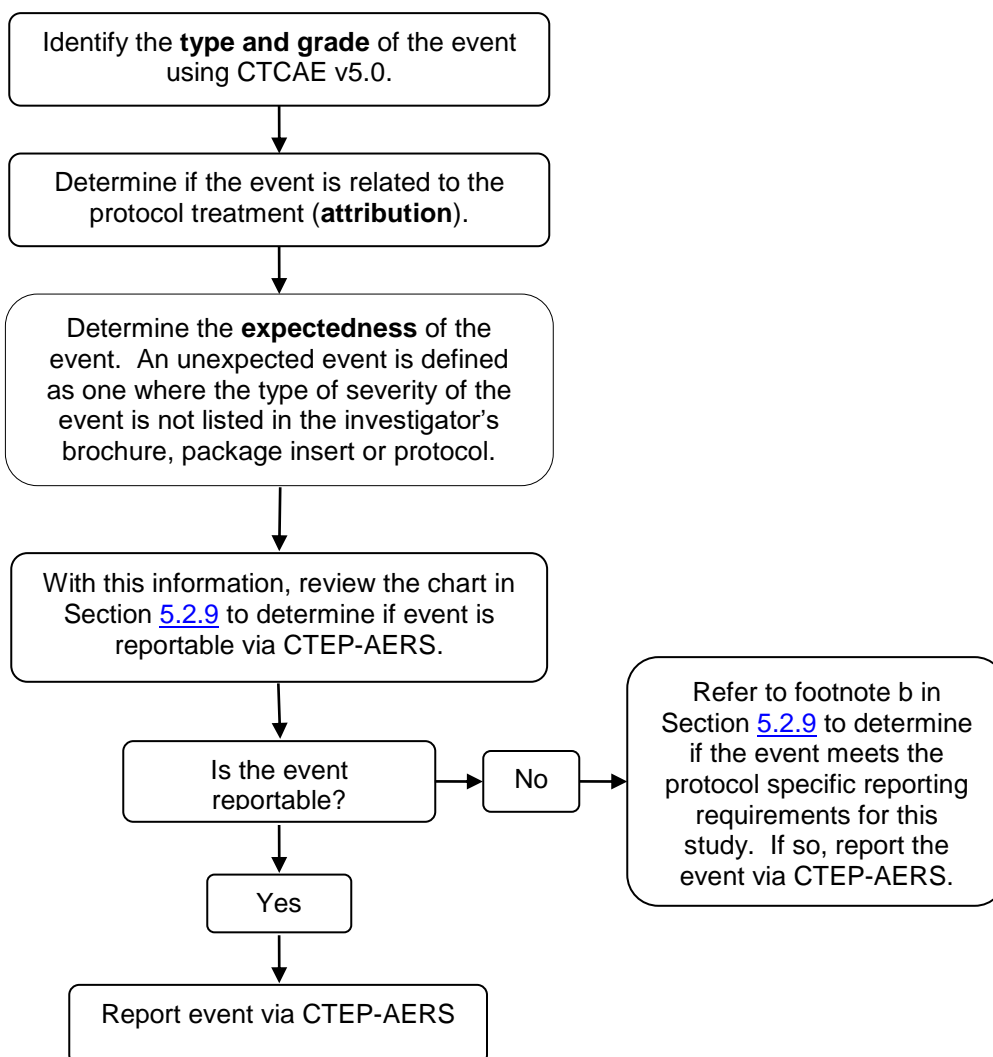
Risk Mitigation Plan:

- Investigators should be vigilant about detecting cases of suspected pulmonary and/or CNS fungal infections and, specifically, aspergillosis.
- If a case of aspergillosis is suspected or observed in this trial, ibrutinib should be discontinued.
- All suspected and confirmed cases of fungal infections should be reported to CTEP within 24 hours.

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5.2.8 **Steps to determine if an event is to be reported in an expedited manner – Arm B**



5.2.9 Expedited Reporting Requirements for Arm B on protocol E1912
Commercial Agents: Fludarabine, Cyclophosphamide, and Rituximab

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only					
Attribution	Grade 4		Grade 5 ^a		ECOG-ACRIN and Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	
7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.					
<p>a This includes all deaths within 30 days of the last dose of treatment regardless of attribution. NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.</p> <p>b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:</p> <p>Serious Events: Any event following treatment that results in <i>persistent or significant disabilities/incapacities, congenital anomalies, or birth defects</i> must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.</p>					

5.2.10 Other recipients of adverse event reports and supplemental data
DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.
Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.11 Second Primary Cancer Reporting Requirements
All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
 1. Complete a Second Primary Form in Medidata Rave within 14 days.

2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
 3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
 1. Complete a Second Primary Form in Medidata Rave within 14 days.
 2. Report the diagnosis via CTEP-AERS at <http://ctep.cancer.gov>
 - *Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy*
 3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
 4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

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NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

Rev. 3/14

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

Rev. 3/14

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for PCI-32765 (Ibrutinib, NSC 748645)

5.3.1 The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ae_guidelines.pdf for further clarification. *Frequency is provided based on 2082 patients.* Below is the CAEPR for ibrutinib (PCI-32765).

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should **ONLY** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

Version 2.6, January 29, 2018¹

Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 5.0 Term) [n= 2082]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		<i>Anemia (Gr 3)</i>
		Blood and lymphatic system disorders - Other (leukostasis) ²	
	Febrile neutropenia		
		Leukocytosis ²	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Ventricular arrhythmia	
		Ventricular fibrillation	
		Ventricular tachycardia	
EYE DISORDERS			
	Blurred vision		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea			<i>Diarrhea (Gr 3)</i>
	Mucositis oral		
	Nausea		<i>Nausea (Gr 2)</i>
	Vomiting		<i>Vomiting (Gr 2)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
	Fatigue		<i>Fatigue (Gr 3)</i>

Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 5.0 Term) [n= 2082]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Fever		
		Sudden death NOS	
HEPATOBIILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIIONS AND INFESTATIONS			
	Infection ³		Infection³ (Gr 3)
		Infections and infestations - Other (bronchopulmonary and central nervous system infections) ⁴	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		
INVESTIGATIONS			
	Lymphocyte count increased ²		
Neutrophil count decreased			Neutrophil count decreased (Gr 4)
	Platelet count decreased		Platelet count decreased (Gr 4)
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
		Hyperuricemia	
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Muscle cramp		
	Myalgia		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (benign neoplasm of skin) ⁵		
		Treatment related secondary malignancy ⁵	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		
		Peripheral sensory neuropathy	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		Cough (Gr 2)
	Dyspnea		

Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 5.0 Term) [n= 2082]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
		Pneumonitis ⁶	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Skin and subcutaneous tissue disorders - Other (angioedema) ⁷	
	Skin and subcutaneous tissue disorders - Other (rash) ⁸		<i>Skin and subcutaneous tissue disorders - Other (rash)⁸ (Gr 3)</i>
		Stevens-Johnson syndrome	
VASCULAR DISORDERS			
	Hypertension		
		Hypotension	
	Vascular disorders - Other (hemorrhage) ⁹		

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

²Leukostasis and/or leukocytosis have been observed especially in patients with chronic lymphocytic leukemia (CLL) and mantle cell leukemia (MCL).

³Infection may include all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

⁴Fungal infections especially respiratory tract infections due to aspergillus and/or pneumocystis and central nervous system (CNS) infections due to aspergillus have been observed in clinical trials of ibrutinib. These reports may include incidents of presumptive fungal infections based on response to anti-fungal agents and/or radiographic evidence.

⁵Other malignant diseases have been observed in patients who have been treated with ibrutinib including solid tumors, skin cancer, and hematological malignancies.

⁶Pneumonitis is included in the group term Interstitial Lung Disease (ILD) which also includes lung infiltration, bronchiolitis, pulmonary fibrosis, eosinophilic pneumonia, pulmonary toxicity, and alveolitis allergic.

⁷Angioedema may be seen in association with the immune-related adverse event of anaphylaxis.

⁸Rash may include but is not limited to the terms dermatitis, erythema, rash generalized, rash maculopapular, rash pustular, rash pruritic, and urticaria.

⁹It is possible that treatment with ibrutinib may increase the risk of hemorrhage which may occur anywhere in the body including CNS hemorrhage (including but not limited to Intracranial hemorrhage, Intraventricular hemorrhage, and Subdural hematoma), Ecchymoses, Purpura (petechia), Gastrointestinal hemorrhage (including but not limited to Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage), Genitourinary tract hemorrhage (including but not limited to Hematuria and Vaginal hemorrhage), Respiratory tract hemorrhage (including but not limited to Epistaxis), and Spontaneous hemorrhage.

Adverse events reported on ibrutinib (PCI-32765) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that ibrutinib (PCI-32765) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hemorrhagic diathesis); Blood and lymphatic system disorders - Other (lymphadenitis); Blood and lymphatic system disorders - Other (pancytopenia); Hemolysis

CARDIAC DISORDERS - Atrial flutter; Atrioventricular block complete; Atrioventricular block first degree; Cardiac disorders - Other (bundle branch block left); Cardiac disorders - Other (extrasystoles); Chest pain - cardiac; Heart failure; Myocardial infarction; Palpitations; Pericardial effusion; Pericarditis; Sinus bradycardia; Supraventricular tachycardia

EAR AND LABYRINTH DISORDERS - Ear pain

EYE DISORDERS - Dry eye; Eye disorders - Other (eye discharge); Eye disorders - Other (macular edema); Eye disorders - Other (ocular hyperemia); Eye disorders - Other (retinal hemorrhage); Eye pain; Floaters; Glaucoma; Keratitis; Periorbital edema; Photophobia; Vision decreased; Watering eyes

GASTROINTESTINAL DISORDERS - Abdominal distension; Cheilitis; Colitis; Dyspepsia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gluteal intramuscular bleed); Gastrointestinal disorders - Other (irritable bowel syndrome); Gastrointestinal disorders - Other (tongue discoloration); Oral dysesthesia; Oral pain; Pancreatitis; Periodontal disease; Small intestinal obstruction; Toothache

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (early satiety); General disorders and administration site conditions - Other (multiple organ dysfunction syndrome); General disorders and administration site conditions - Other (sensation of foreign body); General disorders and administration site conditions - Other (temperature intolerance); Generalized edema; Injection site reaction; Localized edema; Non-cardiac chest pain; Pain

HEPATOBIILIARY DISORDERS - Cholecystitis

IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)

INFECTIONS AND INFESTATIONS - Conjunctivitis

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Infusion related reaction; Injury, poisoning and procedural complications - Other (excoriation)

INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (cardiac murmur); Investigations - Other (increase CRP); Lymphocyte count decreased; Weight gain; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (cachexia); Metabolism and nutrition disorders - Other (hypoproteinemia); Metabolism and nutrition disorders - Other (lactose intolerance)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Flank pain; Generalized muscle weakness; Joint effusion; Joint range of motion decreased; Musculoskeletal and connective tissue disorder - Other (groin pain); Musculoskeletal and connective tissue disorder - Other (muscle rigidity); Musculoskeletal and connective tissue disorder - Other (pain in jaw); Neck pain; Pain in extremity

NERVOUS SYSTEM DISORDERS - Depressed level of consciousness; Dysgeusia; Encephalopathy; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other

(mental impairment); Nervous system disorders - Other (parosmia); Nervous system disorders - Other (PML); Paresthesia; Reversible posterior leukoencephalopathy syndrome; Somnolence; Stroke; Syncope

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Insomnia; Restlessness

RENAL AND URINARY DISORDERS - Cystitis noninfective; Renal and urinary disorders - Other (calculus bladder); Renal and urinary disorders - Other (polyuria); Urinary frequency; Urinary retention; Urine discoloration

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Dyspareunia; Reproductive system and breast disorders - Other (hematospermia); Vaginal dryness

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Hiccups; Laryngeal inflammation; Pleural effusion; Productive cough; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (nasal ulcer); Sinus disorder; Sinus pain; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Nail discoloration; Nail loss; Photosensitivity; Pruritus; Skin atrophy; Skin hyperpigmentation; Skin ulceration; Urticaria

VASCULAR DISORDERS - Flushing; Hot flashes; Thromboembolic event; Vascular disorders - Other (peripheral coldness)

NOTE: Ibrutinib (PCI-32765) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.4 Dose Modifications and Management of Toxicity

Should unanticipated circumstances arise that might require minor variances from the prescribed dosing and schedule of the protocol therapy or recommended supportive care in order to ensure safety and allow patients to continue to receive treatment on study, the ECOG-ACRIN Study Chair should be contacted in advance for discussion and approval.

NOTE: Ibrutinib to be held in the event of major and minor surgeries: major surgeries: Hold ibrutinib for 7 days prior to and seven days after major surgeries. Minor surgeries: Hold Ibrutinib for 3 days prior and 3 days after minor surgeries.

5.4.1 Assessment of Toxicity

- An evaluation of potential treatment-induced toxicity in patients with CLL can be difficult. Moreover, some conventional criteria are not applicable to studies involving patients with hematologic malignancies in general, and CLL in particular. An example is hematologic toxicity: patients with advanced CLL may exhibit a deterioration in blood counts which may represent either treatment-related toxicity or progressive bone marrow failure from disease itself.
- **Toxicity grades below are described using the NCI Common Terminology Criteria for Averse Events (CTCAE) version 4.0 with the exception of hematologic toxicity. Grading Of Hematologic Adverse Events In This Protocol Will Be Performed As Detailed In [Appendix VI](#).**
- All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (<http://ctep.cancer.gov>).
- If the following signs and symptoms are medically manageable, they are not to be a consideration with respect to a patient's dosing or continuation in the study: nausea/vomiting, diarrhea, drug-related fever or chills, and hair loss.

5.4.2 Fludarabine and Cyclophosphamide Dose Levels for Hematologic Dose Modifications Arm B.

NOTE: Patients who require a dose reduction during a given cycle will remain at that dose for future cycles and will not be re-escalated to higher dose levels

If the modifications below indicate that either Fludarabine or Cyclophosphamide should be held, all drugs in the cycle should be held (e.g. the entire cycle delayed) until patient fulfills the indicated criteria for retreatment. Accordingly, there will not be any "missed" doses of medication.

There are no dose modifications for rituximab. If rituximab needs to be held, patients can continue to receive other treatment as prescribed by their assigned arm.

Dose Level	IV Fludarabine Dose Level	Oral Fludarabine Dose Level (Canada Only)	Cyclophosphamide Dose Level
0 (Starting Level)	25 mg/m ² /day	40 mg/m ² /day	250 mg/m ² /day
-1	18.75 mg/m ² /day	30 mg/m ² /day	200 mg/m ² /day
-2	12.5 mg/m ² /day	20 mg/m ² /day	150/m ² /day

5.4.3 Dose Modifications for Neutropenia

Neutrophil growth factors are permitted per American Society of Clinical Oncology (ASCO) guidelines (see Section [5.5.3](#)).

- **Arm A**

For Grade 4 neutropenia (ANC < 0.5 x 10⁹/L [ie, < 500/ μL]) lasting > 7 days, follow the actions outlined in the table:

Occurrence	Action
1 st	Hold Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level (420 mg daily)
2 nd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (280 mg daily)
3 rd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (140 mg daily)
4 th	Discontinue Ibrutinib

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If Ibrutinib is interrupted for a reason on other than toxicity (e.g. unrelated illness) it must be restarted within 60 days. If interrupted for more than 60 days, study medication should be discontinued permanently

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 study documentation.

In patients whose baseline (i.e., prior to starting protocol therapy) ANC is < 1000/μL, the above Ibrutinib dose modifications, if required, would not be applied until Cycle 3.

- **Arm B**

ANC must be ≥ 1000/μL on day 1 of a cycle. For ANC < 1000/μL, hold fludarabine and cyclophosphamide until ANC ≥ 1000/μL, then resume both at one dose level lower than previous dose (see table in Section [5.4.2](#)). If dose reduction to less than dose level -2 is required for neutropenia, discontinue treatment with fludarabine, cyclophosphamide, and rituximab. If fludarabine and cyclophosphamide are delayed for neutropenia, rituximab should also be delayed. If counts have not recovered to adequate levels to permit retreatment by 8 weeks (56 days) from day 1 of the most recent cycle, then the patient will discontinue active treatment.

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NOTE: Patients on Arm B who require a dose reduction during a given cycle will remain at that dose for future cycles and will not be re-escalated to higher dose levels.

In patients whose baseline (i.e., prior to starting protocol therapy) ANC is <1000/ μ L, the FCR dose modifications, if required, would not be applied until Cycle 3.

5.4.4 Dose Modifications for Febrile Neutropenia

- **Arm A**

For febrile neutropenia, hold Ibrutinib until fever resolves and ANC \geq 1000/ μ L, then resume Ibrutinib at the previous dose. If Ibrutinib is delayed for febrile neutropenia, rituximab should also be delayed.

- **Arm B**

For febrile neutropenia, hold fludarabine and cyclophosphamide until fever resolves and ANC \geq 1000/ μ L, then resume both at one dose level lower than the previous dose (see table in Section 5.4.2). If dose reduction to less than dose level -2 is required for febrile neutropenia, discontinue treatment with fludarabine, cyclophosphamide, and rituximab. If fludarabine and cyclophosphamide are delayed for febrile neutropenia, rituximab should also be delayed. If counts have not recovered to adequate levels to permit retreatment by 8 weeks (56 days) from day 1 of the most recent cycle, then the patient will discontinue active treatment.

NOTE: Patients on Arm B who require a dose reduction during a given cycle will remain at that dose for future cycles and will not be re-escalated to higher dose levels

5.4.5 Dose Modifications for Thrombocytopenia

- **Arm A**

Grade 3 thrombocytopenia (platelets $<50 \times 10^9/L$ [ie, $< 50,000/mL$]); or in subjects with baseline thrombocytopenia a platelet decrease of 50% to 74% from baseline that is associated with clinically significant bleeding follow the actions outlined in the table:

Occurrence	Action
1 st	Hold Ibrutinib until recovery to Grade \leq 1 or baseline; may restart at original dose level (420 mg daily)
2 nd	Hold Ibrutinib until recovery to Grade \leq 1 or baseline; restart at 1 dose level lower (280 mg daily)
3 rd	Hold Ibrutinib until recovery to Grade \leq 1 or baseline; restart at 1 dose level lower (140 mg daily)
4 th	Discontinue Ibrutinib

For grade 4 thrombocytopenia (platelets $< 25 \times 10^9/L$ [ie, $< 25,000/mL$]); or in subjects with baseline thrombocytopenia a decrease of $> 75%$ from baseline or $< 20 \times 10^9/L$, whichever is higher (note Section 5.1.1.1 for those with a baseline platelet count less than $20 \times 10^9/L$) follow the actions outlined in the table:

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Occurrence	Action
1 st	Hold Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level (420 mg daily)
2 nd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (280 mg daily)
3 rd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (140 mg daily)
4 th	Discontinue Ibrutinib

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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 study documentation.

• **Arm B**

Platelets must be ≥ 100,000/μL or > 80% of baseline value (i.e., > 80% of the value before protocol therapy started) on day 1 of a cycle. For platelets < 100,000/μL or < 80% of baseline, hold fludarabine and cyclophosphamide until platelets ≥ 100,000/μL or > 80% of baseline, then resume both at one dose level lower than the previous dose. If dose reduction to less than dose level -2 is required for thrombocytopenia, discontinue treatment with fludarabine, cyclophosphamide, and rituximab. If fludarabine is delayed for thrombocytopenia, rituximab should also be delayed. Note Section [5.1.3.1](#) for those with a baseline platelet count less than 20x10⁹/L. If counts have not recovered to adequate levels to permit retreatment by 8 weeks (56 days) from day 1 of the most recent cycle, then the patient will discontinue active treatment.

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In patients whose baseline (i.e., prior to starting protocol therapy) platelet count < 100,000/μL, these dose modifications, if required, would not be applied until Cycle 3.

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5.4.6 Dose Modifications for Atrial Fibrillation (Arm A)

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.

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 study documentation.

5.4.7 Autoimmune Hemolytic Anemia or Thrombocytopenic Purpura

Patients on Arm B developing autoimmune hemolytic anemia (AIHA) or autoimmune thrombocytopenia (AIT) during fludarabine therapy will be removed from protocol therapy, and treated with alternative agents at the discretion of the local physician. In this event, please consult with the ECOG-ACRIN Study Chair.

NOTE: Patients remain “on study” until an endpoint, either progression or death, is reached.

5.4.8 Non-Hematologic Toxicity (not including nausea, vomiting, diarrhea, drug-related chills and hair loss except where specified)

- If multiple adverse events are seen, administer dose based on the greatest reduction required by any single adverse event observed.
- Dose modifications are for adverse events attributed to study treatment. Dose modifications are not required for adverse events unrelated to study treatment.
- Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- If Ibrutinib is interrupted for a reason other than toxicity (e.g. unrelated illness) the first instance of interruption must be restarted within 42 days. Subsequent study medication interruptions lasting more than 42 days ibrutinib should be discontinued permanently.
- 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 study documentation.
- If cough, dyspnea, and other pulmonary symptoms occur, a chest x-ray and high-resolution chest CT scan should be obtained. Incentive spirometry studies (to include DLCO).should be considered. Consider Pneumocystis pneumonia or viral pneumonitis.
- If treating provider feels that a dose reduction needs to be made based on first occurrence (e.g. without restarting at original dose level) this must be discussed with study PI who can who can approve this request at their discretion.
- **Arm A**
 - Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic or anti-diarrheal therapy) or any other Grade 4 toxicity or any unmanageable Grade 3 toxicity follow the actions outlined in the table:

Occurrence	Action
1 st	Hold Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level (420 mg daily)
2 nd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (280 mg daily)
3 rd	Hold Ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (140 mg daily)
4 th	Discontinue Ibrutinib

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

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reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the study documentation.

- **Arm B**

- For non-hematologic toxicity \geq grade 2 attributable to fludarabine, reduce fludarabine by 50%.
- For non-hematologic toxicity \geq grade 2 attributable to cyclophosphamide, reduce cyclophosphamide by 50%.
- If cough, dyspnea, and other pulmonary symptoms occur, a chest x-ray and high-resolution chest CT scan should be obtained. Incentive spirometry studies (to include DLCO).should be considered. Consider Pneumocystis pneumonia or viral pneumonitis.

5.4.9 Anti-coagulant therapy for patients on Arm A

Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g., atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted. For this study, non-vitamin K based anti-coagulation is preferred. If Coumadin or other vitamin K antagonist is being considered, it should be discussed with the study chair.

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5.4.10 Infusion reactions

As discussed in [5.1.1.5](#) (Arm A) and [5.1.3.4](#) (Arm B), rituximab infusion reactions are relatively common and in most patients can be managed with interruption of the infusion, supportive measures, and reinitiation of rituximab at a slower rate of infusion once symptoms resolve. Based on multiple phase 3 trials showing inclusion of anti-CD20 impacts overall survival of CLL patients receiving first-line treatment, effort should be made to incorporate the supportive measures in [5.1.1.5](#) (Arm A) and [5.1.3.4](#) (Arm B) and continue to include rituximab in the treatment regimen rather than omit this agent. In the rare circumstances where severe recurrent infusion reactions or other severe rituximab related toxicity occurs (e.g. rituximab induced pneumonitis), rituximab may be omitted and the remaining agents (Arm A: Ibrutinib, Arm B: fludarabine and cyclophosphamide) continued if deemed appropriate by the treating physician. Such cases should be discussed with the study Principle Investigator.

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5.4.11 Dose Modification for Hepatic Impaired Subjects (Child-Pugh Criteria) for Arm A

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child-Pugh class B or C) are excluded from study participation. Please see the Child-Pugh scoring system outlined in Appendix G to determine whether dose modifications are warranted according to the

following instructions. For patients who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose for ibrutinib is 280 mg daily (two capsules). For patients who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose is 140 mg daily (one capsule). Patients who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better and may be re-treated according to resolved hepatic conditions (i.e., 140 mg or 280 mg for moderate or mild impairment, respectively). Monitor patients for signs of toxicity and follow dose modification guidance as needed.

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5.5 Supportive Care

- 5.5.1 All patients must receive daily allopurinol (300 mg/day PO) for days 1-14 of cycle 1 of therapy on both treatment arms unless they are allergic. Patients on Arm A (Ibrutinib/Rituximab) will also receive allopurinol (300 mg/day PO) for days 1-14 of cycle 2 since that is the first cycle they receive rituximab. The need for allopurinol with subsequent induction cycles is left to the discretion of the treating physician. For patients with an allergy to allopurinol that precludes administration, patients can be followed closely for tumor lysis syndrome without allopurinol and the use of rasburicase as needed at the discretion of the treating physician.
- 5.5.2 Patients on both study arms will receive Bactrim DS 1 tablet (or alternative Pneumocystis pneumonia prophylaxis) on Monday/Wednesday/Friday AND acyclovir 400 mg p.o. twice per day (or equivalent) beginning with cycle 1 and continuing until the time of response evaluation (52 weeks after start of cycle 1; see Section [7.1](#)). Even if patients discontinue protocol treatment, they should remain on these prophylactic anti-biotics until this timepoint.
- 5.5.3 Neutrophil growth factors are permitted per American Society of Clinical Oncology (ASCO) guidelines (JCO 24:3187-3205). Use of colony stimulating factors (e.g., filgrastim, sargramostim, PEG-filgrastim) in this protocol is permitted during therapy as required for the treatment of febrile neutropenia. Colony stimulating factors may not be used to avoid dose reductions (e.g. to boost counts immediately before a starting a treatment cycle). The use of colony stimulating factors must be noted on flow sheets.
- 5.5.4 Any blood transfusions administered must be irradiated blood products to reduce risk of transfusion mediated graft versus host disease in CLL patients receiving potentially T-cell suppressive therapy.
- 5.5.5 All supportive measures consistent with optimal patient care will be given throughout the study.
- 5.5.6 As of 2012, the Center for Disease Control (CDC) recommends routine use of the 13-valent pneumococcal conjugate vaccine (PCV12; Prevnar 13) for all adults with CLL and other immunocompromising conditions. Per the CDC, this should be administered **in addition to** the standard 23-valent pneumococcal

vaccine (PCV-23; Pneumovax 23) received by most adults. Since most CLL patients have not yet received Prevnar 13, all study patients who have:

- i) not previously received the Prevnar 13 pneumococcal vaccine
- ii) are \geq 12 months from their last Pneumovax (or have never received a Pneumovax)
- iii) are willing to receive vaccination

should receive Prevnar 13 vaccination at the time of their 12 month response evaluation. Additional information on the CDC guidelines can be found at:

<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm>

- 5.5.7 Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith et al., 2006).

Short courses (\leq 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 100 mg per day of prednisone or equivalent are permitted.

Treatment for autoimmune cytopenias for patients on Arm A are permitted for at doses that do not exceed 100 mg per day of prednisone or equivalent. Patients on Arm B who develop autoimmune cytopenias must discontinue therapy as per 5.4.7.

The following may be considered: localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

- 5.5.8 If a strong CYP3A inhibitor must be used, reduce ibrutinib dose to 140 mg or withhold treatment temporarily. Patients should be monitored for signs of ibrutinib toxicity. If a moderate CYP3A inhibitor must be used, reduce ibrutinib to 140 mg for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Please [Appendix VIII](#) for a list of CYP3A inhibitors.

- 5.5.9 Any medications known to cause QT prolongation should be used with caution; periodic monitoring with electrocardiograms (ECGs) and electrolytes should be considered.

- 5.5.10 In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp) or other transporters, except OCT2. Ibrutinib is a mild inhibitor of P-gp and 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; therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp or BCRP substrates such as digoxin or methotrexate, should be taken at least 6 hours before or after ibrutinib. Inhibition of the BCRP pathway may increase exposure to drugs that undergo BCRP mediated hepatic efflux, such as rosuvastatin.

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

For major surgery ibrutinib should be held for at least 3 days prior to the procedure and should be held after the procedure until the surgical site is reasonably healed, or for at least 7 days after the surgical procedure, whichever is longer.

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

5.5.12 Leukocytosis/Leukostasis

A high number of circulating malignant cells (>400,000/mcL) may confer increased risk of leukostasis; these patients should be closely monitored. Administer supportive care such as hydration and/or leukopheresis as indicated. Ibrutinib should be temporarily held, and study principle investigator should be contacted.

5.5.13 Supplements such as fish oil and vitamin E preparations should be avoided.

5.6 Duration of Therapy

Patients will receive protocol therapy unless:

5.6.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E1912 Forms Completion Guidelines.

5.6.2 Patient withdraws consent.

5.6.3 Patient experiences unacceptable toxicity.

5.6.4 Non-protocol therapies are administered.

5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 10 years from the date of registration. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

Patients should be reevaluated for progression every 4 weeks (+/-10 days) during the first 6 months of the study by physical exam and CBC. Although formal response evaluation will not occur until the 12 month response evaluation (or off study evaluation), patients will be evaluated prior to cycles 1-6 and 3 months after the end of cycle 6 of therapy to identify individuals who have experienced disease progression.

Prior to the formal response evaluation, baseline on study measurements will be used to determine disease progression (e.g. NOT cycle by cycle comparisons). Once patients undergo formal response evaluation, the nadir value at either baseline or time of response will be used for evaluating future disease progression.

NOTE: With the exception of SLL patients without palpable lymph nodes (see Section [6.1.1.1](#)) Information from CT scans is not considered in the standard classification of response which is based on the results of CBC, physical exam, and bone marrow examination. Accordingly, data from CT scans will be collected to document response and or persistence of non-palpable nodes at the time of formal response evaluation but will not be used in the primary response categorization.

6.1 Assessment of Clinical Response

The major criteria for determination of the response to therapy in patients with CLL are based on physical examination and evaluation of peripheral blood and bone marrow. It is recommended that the laboratory and radiographic studies which are abnormal pre-study be repeated to document the degree of maximal response.

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Physical exam must measure the spleen and liver noting the maximal distance below the respective costal margins at rest in the mid-clavicular line and must record the bidimensional diameter of the *largest* palpable node in each lymph node area of involvement including the following 6 sites: cervical/supra-clavicular (right and left) axillary (right and left), inguinal (right and left).

6.1.1 Complete remission requires all of the following for a period of at least 2 months (e.g. 2 occasions at least 4 weeks apart):

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6.1.1.1 Absence of lymphadenopathy by physical examination on 2 occasions at least 4 weeks apart and appropriate radiographic techniques (e.g. all lymph nodes \leq 1.5 cm). For patients whose only measurable disease at the time of enrollment is on CT scan (i.e. SLL with no palpable nodes), a CT scan is required and all lymph nodes must be \leq 1.5 cm before classifying the patient a CR.

6.1.1.2 Absence of hepatomegaly or splenomegaly by physical examination.

6.1.1.3 Absence of constitutional symptoms (fevers, nights sweats, weight loss, fatigue) due to disease.

6.1.1.4 Normal CBC as exhibited by:

6.1.1.4.1 Polymorphonuclear leukocytes \geq 1500/ μ l.

6.1.1.4.2 Platelets $>$ 100,000/ μ l (untransfused).

6.1.1.4.3 Hemoglobin > 11.0 gm/dl (untransfused).

6.1.1.4.4 Peripheral blood lymphocytes \leq 4000/ μ l.

NOTE: Patients who fulfill all criteria for a CR but who have a persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity rather than residual CLL will be classified as CR with incomplete marrow recovery (CRi) according to the international criteria.

6.1.1.5 One marrow aspirate and biopsy should be performed 52 weeks after Day 1 of cycle 1 (see Section [7.1](#)) among patients with clinical and laboratory evidence of a CR to document that a complete remission has been achieved. The marrow sample must be at least normocellular with < 30% of nucleated cells being lymphocytes. If it is hypocellular, a repeat determination should be made in 2-4 weeks. Samples are to be analyzed by a pathologist and the presence or absence of nodules noted, although not included in the current definition of CR. Only a single BM exam is needed to document CR.

NOTE: In a subset of patients who are otherwise in a CR, bone marrow nodules can be identified histologically. In such cases, special stains will be performed to determine whether such nodules represent “regenerative nodules” or residual “clonal nodules”. The presence of regenerative nodules is consistent with CR while the presence of residual clonal nodules will be classified as a nPR (nodular PR) which is a sub-classification of PR.

6.1.1.6 Any other laboratory assays (e.g., quantitative immunoglobulins) will not be used currently as an index for response but will be recorded for clinical correlations.

6.1.2 To be considered in PR, the patient must exhibit the features in Sections [6.1.2.1](#), [6.1.2.2](#), and [6.1.2.3](#) (if abnormal prior to therapy) as well as one or more of the remaining features (Sections [6.1.2.4](#), [6.1.2.5](#), [6.1.2.6](#)) for at least 2 months (e.g. 2 occasions at least 4 weeks apart). In addition to the parameters listed below, the presence or absence of constitutional symptoms will be recorded.

6.1.2.1 \geq 50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value.

6.1.2.2 \geq 50% reduction in lymphadenopathy. For patients whose only measurable disease at the time of enrollment is on CT scan (i.e. SLL with no palpable nodes), a CT scan

- demonstrating $\geq 50\%$ reduction of target nodes enlarged at baseline is required before classifying the patient a PR.
- 6.1.2.3 $\geq 50\%$ reduction in size of liver and/or spleen as measured by physical exam noting the maximal distance below the respective costal margins of the palpable hepatosplenomegaly during rest.
 - 6.1.2.4 Polymorphonuclear leukocytes $\geq 1500/\mu\text{l}$ or 50% improvement over baseline.
 - 6.1.2.5 Platelets $> 100,000/\mu\text{l}$ or 50% improvement over baseline.
 - 6.1.2.6 Hemoglobin $> 11.0 \text{ gm/dl}$ or 50% improvement over baseline without transfusions.

6.1.3 Progressive disease (PD)

Progressive Disease (PD) will be characterized by at least one of the following:

- 6.1.3.1 $\geq 50\%$ increase from nadir value since start of treatment in the sum of the products of at least 2 lymph nodes on 2 consecutive examinations 2 weeks apart (at least 1 node must be $\geq 2 \text{ cm}$) and that is not due to tumor flare reaction. Appearance of new palpable lymph nodes $> 1.5 \text{ cm}$ not due to tumor flare reaction.
- 6.1.3.2 $\geq 50\%$ increase from nadir value since start of treatment in the size of liver and/or spleen as determined by measurement below the respective costal margin that is not due to tumor flare reaction. Appearance of palpable hepatomegaly or splenomegaly which was not previously present that is not due to tumor flare reaction.
- 6.1.3.3 $\geq 50\%$ increase in the absolute number of circulating lymphocytes (taking as a reference for progressive disease the smallest absolute lymphocyte count recorded since the treatment started) not due to tumor flare reaction. The absolute lymphocyte count must be at least $5 \times 10^9/\text{L}$ to qualify as disease progression.

NOTE: It is common for CLL patients to experience a transient increase in lymphocytosis due to redistribution of lymphocytes from the lymph nodes and spleen to the peripheral blood circulation. This lymphocytosis is NOT a marker of disease progression or Richter's transformation and typically resolves over several months. For this reason, prior to the 12 month response evaluation, patients on both arms will not be considered to have disease progression based on an increased absolute lymphocyte count if they simultaneously have unequivocal improvement in at least one other disease-related parameter including lymph node size, spleen size,

hematologic parameters (Hgb or platelet count), or disease-related symptoms. Questions regarding an increase in the absolute lymphocyte count after initiation of therapy should be discussed with the study PI.

6.1.3.4 **Unscheduled CT Scans:** Since this is an open label trial, it is possible that an imbalance in unscheduled CT scans could emerge between arms and influence assessment of disease progression. To address this issue, all unscheduled CT scans performed on both arms as well as the reason for unscheduled CT scans will be recorded. This information will be collected to identify differences in the frequency of such unscheduled CT scans between arms and allow us to detect potential bias in ascertainment of disease progression (see Section 9.3.1.2).

6.1.3.5 **Progression by physical exam only:** It is anticipated that most cases of disease progression will initially be identified by an objective increase in the absolute lymphocyte count (ALC) on a complete blood count or simultaneous increase in ALC and progressive lymphadenopathy.

Given the unblinded nature of the trial however, it is possible that a difference in the interpretation of palpable lymphadenopathy could occur between arms. To address this possibility, we will record the pattern of relapse by classifying all patients experiencing progression as:

- Progression due to rising ALC only
- Progression determined by lymphadenopathy on physical exam only
- Progression due to both rising ALC and physical
- Exam

This information will be evaluated to identify potential bias due to differences in the interpretation of palpable lymphadenopathy between arms (Section [9.3.3](#)).

6.1.3.6 In the absence of progression as defined above, the presence of a ≥ 2 gm/dl decrease in hemoglobin, or $\geq 50\%$ decrease in platelet count and/or absolute granulocyte count will not exclude a patient from continuing on study. Bone marrow aspirate and biopsy are strongly encouraged to better define the cause of the suppressed counts.

6.1.3.7 Transformation to a more aggressive histology (e.g. Richter's syndrome or prolymphocytic leukemia with $> 55\%$ prolymphocytes).

6.1.3.8 For patients who achieve a CR or nodular PR < progression will be defined as recurrence of circulating leukemia cell clone in the peripheral blood and an absolute

- lymphocyte count $> 5 \times 10^9/L$ and/or recurrence of palpable lymphadenopathy > 1.5 cm by physical exam.
- 6.1.4 Stable Disease (SD)
- 6.1.4.1 Patients who have not achieved a CR or a PR, or who have not exhibited findings consistent with Progressive Disease will be considered as having Stable Disease.
- 6.1.5 Complete Clinical Remission (CCR)
- 6.1.5.1 Patients who have clinical and laboratory evidence of CR but who have not yet had a bone marrow biopsy to distinguish between CR and nPR will be classified as having a complete clinical response (CCR) until the marrow biopsy is obtained.
- 6.1.6 Evaluation of Minimal Residual Disease (MRD): An important aspect of this trial is that evaluation of minimal residual disease using a sensitive flow cytometry method capable of detecting approximately 1 CLL cell per 10,000 leukocytes following induction.

An International, standardized approach for flow cytometric evaluation of residual disease in patients with CLL was recently developed (32). This approach reliably detects residual CLL B-cells at the level of 1 leukemic cell per 10,000 leucocytes. Notably, analysis of peripheral blood was equally or more sensitive to marrow in 92% of samples except when patients had received treatment with monoclonal antibodies (such as rituximab) within 3 months of evaluation.

This approach uses a pre-antibody ammonium chloride red cell lysis approach to separate peripheral blood white blood cells from RBCs followed by staining of $1-2 \times 10^6$ leukocytes with a panel of antibodies for flow cytometry analysis. For each test, 300,000 to 500,000 events were collected to ensure the desired sensitivity of the assay.

While the 4 color based strategy was the standard proposed by the international group, 5- to even 8-color flow cytometry based assays are being used in many laboratories and are expected to have a similar degree of sensitivity (level of 1 leukemic cell per 10,000 leucocytes) while enhancing the accuracy of the assay.

Assessments for MRD in the present study will be conducted as a research assay in the Mayo Clinic Rochester Department of Hematopathology under the direction of Dr. Curtis Hanson using a flow cytometry strategy able to detect residual leukemia at the level of 1 leukemic cell per 10,000 leukocytes in accord with the International Standard (32). For each test, 200,000 to 500,000 events are collected to ensure the desired sensitivity of the assay.

All patients will undergo assessment of MRD using sensitive flow cytometry 52 weeks (+/- 14 days) after day 1 of cycle 1 (see Section 7.1). Since the assessment of MRD 52 weeks after day 1 of cycle 1 will occur more than 3 months of rituximab therapy, MRD assays will be performed on peripheral blood. MRD testing for research purposes will be performed at other time-points as indicated in Section 7.

6.1.7 Quality of Life

CLL and CLL treatment can have a substantial affect on patient quality of life.

While Ibrutinib appears to have a favorable toxicity profile relative to fludarabine based therapy, the need for chronic indefinite administration may result in chronic side effects that ultimately erode QOL over the long run (compared to a more intense but limited duration treatment schedule). In addition, the benefit of lower toxicity may not ultimately improve QOL if this treatment is less effective at controlling the disease.

To explore these aspects, the present study is designed to assess the QOL of patients on both treatment arms longitudinally. Mandatory quality of life will be assessed at the following 8 time-points:

- Baseline
- After 3 cycles of therapy
- After 6 cycles of therapy
- At response evaluation (52 weeks after day 1 of cycle 1)
- Every 6 months for 2 years after response evaluation
- At disease progression

The QOL of patients in the treatment arms will be compared at these time points to assess affect of treatment arm on QOL both during active the first several months of treatment and over the long term.

Primary Endpoint

Quality of life (QOL) will be assessed using FACT-G and the leukemia subscale. The primary objective of the QOL study is to compare treatment toxicity-related QOL in patients receiving the experimental Ibrutinib -based therapy to those receiving standard FCR. The primary interest is the FACT-Leu Trial Outcome Index (TOI), which is comprised of the FACT-G physical well-being (PWB) and functional well-being (FWB) subscales and the leukemia subscale. The FACT-Leu TOI contains a total of 31 items, with scores ranging from 0 to 124. It will be administered at the following time points: at the time of randomization, three months and six months after randomization, and every six months thereafter. The primary endpoint is the change in FACT-Leu TOI score from the time of randomization to 12 months after beginning therapy between the FCR arm and the Ibrutinib arm.

To better understand the impact of CLL on an individual's QOL, the entire FACT-G Leukemia questionnaire will be administered to all patients at the time of study enrollment, i.e., prior to initiating therapy. The FACT-G Leukemia is a 43-item instrument, containing the subscales previously described above. In addition, it also contains a social and an emotional well-being subscale.

Adherence:

In addition to longitudinally measuring QOL, we will also assess adherence to therapy in the Ibrutinib arm given that it is a chronic oral

therapy. Adherence will be assessed using both the pill diary ([Appendix III](#)) completed with each cycle as well as the Morisky Adherence Scale.). The Morisky scale will be completed by patients on the Ibrutinib arm at treatment cycle 3, treatment cycle 6, month 12 (52 week) and month 24.

7. Study Parameters

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7.1 Therapeutic Parameters

1. Prestudy scans or x-rays used to document measurable or evaluable disease must be done within 2 weeks of registration.
2. Prestudy CBC with differential, LFTs must be done ≤ 2 weeks before registration.
3. All required prestudy chemistries must be done ≤ 2 weeks before registration - unless specifically required on Day 1 as per protocol. If abnormal, they must be repeated within 48 hours prior to registration.

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Tests/Procedures	Active Monitoring Phase						
	Pre-treatment	During Treatment ¹⁴			12 Month Response Evaluation	Continuation ¹⁷	Follow Up ¹⁵
	≤ 14 days prior to registration	Day 1 of Cycles 1-6 (+/- 4 days) ¹⁹	Prior cycle 7 (arm A) or End of Cycle 6 (arm B) (+/- 4 days)	3 months after end of cycle 6 (+/- 7 days)	52 weeks after Day 1 of cycle 1 (+/- 4 weeks)	Every 90 days (+/- 14 days)	
Tests & Observations							
History and progress note ¹⁴	X	X ¹⁸	X	X	X	X	X
Performance status ¹⁴	X	X ¹⁸	X	X	X	X	
Height	X						
Weight/Body Surface Area ¹	X	X			X		
Physical examination ¹⁴	X	X ¹⁸	X	X	X	X	X
Tumor measurement by physical exam ¹⁴	X ²	X ^{2, 18}	X ²	X ²	X ²	X ²	X ²
Drug toxicity measurement ¹⁴	X	X ¹⁸	X	X	X	X	
Comorbidity Index	X ³						
Timed Up and Go (TUG) Test ¹³	X						
Laboratory Studies							
CBC with differential ^{5,14}	X	X ⁴	X ⁴	X	X	X	X
Serum creatinine and creatinine clearance ¹⁶	X	X ⁵					
Uric acid, potassium, phosphate, LDH, Ca+	X	X ⁵					
AST, ALT, total bilirubin, alkaline phosphatase ¹⁴	X	X	X	X	X	X	
Peripheral blood immunophenotyping by flow cytometry on peripheral blood or bone marrow ⁷	X						
Serum pregnancy test	X ⁶						
CLL FISH panel (on peripheral blood or bone marrow aspirate)	X ⁷						
Bone marrow aspirate and biopsy ¹⁴	X ⁸				X ⁸		
Beta-2-microglobulin ¹⁴	X				X		

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Tests/Procedures	Active Monitoring Phase						
	Pre-treatment	During Treatment ¹⁴			12 Month Response Evaluation	Continuation ¹⁷	Follow Up ¹⁵
	≤ 14 days prior to registration	Day 1 of Cycles 1-6 (+/- 4 days) ¹⁹	Prior cycle 7 (arm A) or End of Cycle 6 (arm B) (+/- 4 days)	3 months after end of cycle 6 (+/- 7 days)	52 weeks after Day 1 of cycle 1 (+/- 4 weeks)	Every 90 days (+/- 14 days)	
PT/INR, PTT (aPTT)	X						
Quantitative Immunoglobulins (IgG, IgA, IgM) ¹⁴	X				X		
Hepatitis B (HB) surface antigen, surface Ab and core Ab testing;	X ⁹						
Hepatitis C Anti-body testing	X ¹¹						
Direct Coombs test	X						
CT scan chest, abdomen, pelvis ¹²	X				X		
Biological Sample Submissions	See Section 7.2						
QOL Questionnaires ^{10, 14}	X ¹⁰	X ¹⁰	X ¹⁰		X ¹⁰	X ¹⁰	X ¹⁰

Footnotes for Test Schedule

1. Drug doses need not be changed unless the calculated dose changes by >10%
2. Physical exam must measure the spleen and liver noting the maximal distance below the respective costal margins at rest in the mid-clavicular line and must record the bidimensional diameter of the largest palpable node in each lymph node area of involvement including the following 6 sites: cervical/supra-clavicular (right and left) axillary (right and left), inguinal (right and left).
3. Cumulative illness rating scale – see [Appendix VII](#) (JCO 16: 1582–1587).
4. For cycle 1, patients with pretreatment platelet counts < 20x10⁹/L, should have a CBC repeated on Day 3. If this platelet count is below 20x10⁹/L, the responsible physician should be contacted and platelets should be transfused, if clinically indicated. As treatment with anti-CD20 monoclonal anti-bodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts < 50x10⁹/L prior to receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.
5. In Arm B patients, all tests noted should be collected prior to treatment on Day 2 of Cycle 1 to monitor for tumor lysis.
6. For women of childbearing potential only. Must be done ≤ 14 days prior to registration.
7. Must be done ≤ 3 months prior to registration. It is acceptable for FISH to be performed on either peripheral blood or bone marrow tissue.
8. Bone marrow biopsy is required. If the patient has had a bone marrow biopsy obtained for clinical purposes ≤ 3 months prior to registration this can be used for baseline purposes and a repeat is not required provided slides from this clinical bone marrow can be submitted. At time of response evaluation a bone marrow biopsy is required for all patients with evidence of response (CR, PR) or stable disease but is not required for those with disease progression. Bone marrow slides for central review must be submitted as outlined in Section [10](#).
9. All patients must be screened for hepatitis B infection before starting treatment. Those patients who test positive for hepatitis B are ineligible. Tests must be done ≤ 4 weeks prior to registration. See Section [3.1.18](#).

-
- Rev. 7/14 10. Quality of life will be evaluated at baseline, after the first 3 cycles of therapy; after 6 cycles of therapy; at the time of the 12 month response evaluation, and then every 6 months for 2 years regardless of whether or not the patient progresses. QOL will also be assessed at the time the patient progresses
11. If Hepatitis C anti-body testing is positive, PCR to evaluate active Hepatitis C. Patients with active Hepatitis C are ineligible (see Section [3.1.17](#)). Tests must be done \leq 4 weeks prior to registration.
12. Baseline CT scan requirement can be waived if the patient has had a CT scan \leq 4 weeks prior to registration. In such cases, the clinical CT scan obtained within the last 4 weeks may serve as the baseline CT scan for measurement purposes. At time of response evaluation CT scan of the chest, abdomen and pelvis is required for all patients with evidence of response (CR, PR) or stable disease but is not required for those with disease progression.
13. Please see [Appendix X](#) for instructions for the Timed Up and Go (TUG) Test.
- Rev. 3/14, Rev. 11/16 14. If patient comes off treatment due to any reason other than progression or completion of treatment per protocol (Arm B), please complete all of the noted tests/procedures with 2 weeks in lieu of a 12 Month Response Evaluation.
- Rev. 3/14 15. Every 3 months (90 days) until progression. After progression, patient will switch to standard follow-up schedule: every 3 months for first 2 years, every 6 months for years 3-5, and then every 12 months for years 6-10.
- Rev. 7/14 16. Creatinine clearance as estimated by the Cockcroft-Gault equation. See Section [3.1.9](#)
17. All patients on Arm A currently taking Ibrutinib
18. If pre-registration value is $<$ 21 days from treatment start date, test does not need to be repeated on day 1 cycle 1.
19. Laboratories required on day 1 of cycles 1-6 of Arm B should be collected prior to start of chemotherapy. For patients on Arm A, these laboratories should be collected prior to the start of rituximab.

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7.2 Biological Sample Submissions

1. Bone marrow sections/slides and smears must be submitted for central histological review at baseline and at the time of the twelve (12) month response evaluation as outlined in Section [10](#).
2. Peripheral blood and buccal cells should be submitted as outlined below for correlative studies and/or banking, per patient consent.

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG-ACRIN Operations Office – Boston regarding logistics for submission of fresh samples.

NOTE: Patients must sign informed consent before the submission of the samples. If submitting baseline samples prior to patient enrollment to the trial, please use the Generic Specimen Submission Form (#2981) and call the receiving laboratories prior to shipping. Once the patient is randomized please call the receiving laboratories with the ECOG-ACRIN patient sequence number and retroactively log the sample information into the ECOG-ACRIN Sample Tracking System.

NOTE: It is required that biological sample submissions be logged into the ECOG-ACRIN Sample Tracking System (STS) (see Section [10.4](#)) for purposes of monitoring compliance.

NOTE: Please note there are sample submissions to **two** separate laboratories.

Rev. 7/14, 8/15	Biological Materials	Baseline	After Three (3) Cycles of Therapy	After Six (6) Cycles of Therapy [Prior to Cycle Seven (7) Arm A, End of Cycle Six (6) Arm B]	Twelve (12) Month Response Evaluation (52 weeks after day 1 of cycle 1)	15, 18, 24, and 36 months after randomization	Time of Disease Progression or Relapse	Ship To:
MANDATORY for Central Review								
Rev. 11/16	Bone Marrow Biopsy Sections/Slides ⁵	X			X			LTRL ²
	Bone Marrow Smears (Wright-Giemsa stained)	X ¹						LTRL
From Patients Who Answer "YES" to "I agree to participate in the laboratory research studies that are being done as part of this clinical trial."								
	Peripheral Blood (sodium heparin (5) 10mL green top tubes)	X ¹	X	X	X	X	X	Mayo Clinic ³
	Peripheral Blood (serum, (2) 10mL red top tubes)	X ¹			X	X ⁷		Mayo Clinic ³
From Patients Who Answer "YES" to "I agree to provide additional specimens for research."								
	Peripheral Blood (serum, (2) 10mL red top tubes, 15-20mL)	X ¹						LTRL
	Peripheral Blood (heparin, (4) 10mL green or purple [EDTA] top tubes, 30-40mL)	X ¹						LTRL
	Buccal Rinse (preferred) or Swab ⁶	X ¹						LTRL

1. After randomization, prior to treatment.
2. Submit to the ECOG-ACRIN Leukemia Translational Research Laboratory (LTRL). Signed E1912 patient consents and HIPAA authorizations must be submitted to the LTRL prior to or at time of submission of baseline samples per Dr. Paietta's institutional regulations.
3. Collection and shipping kits are being provided for the peripheral blood being submitted to Mayo Clinic.
4. [Deleted in Addendum #2]
5. Bone marrow biopsy sections/slides for central review can be from the clinical biopsy performed within three (≤ 3) months prior to registration if the on-study baseline bone marrow biopsy was not performed. Sections/slides are to be submitted within one (1) month of randomization.
6. Buccal rinse (preferred) or swabs are strongly encouraged to be collected prior to the start of treatment, but can be collected at any other time during the study, if necessary.
7. Collect at month 15 only.

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8. Drug Formulation and Procurement

Drug Ordering: *Pharmacyclics* is supplying Ibrutinib (PCI-32765), through the Division of Cancer Treatment and Diagnosis, NCI, for this protocol. Maintenance of NCI drug accountability records is required. Ibrutinib (NSC 748645 IND 117241) may be requested by the Principal Investigator (or their authorized designees) at each participating institution.

The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (<https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx>). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (<https://eapps-ctep.nci.nih.gov/iam/>) and the maintenance of an “active” account status and a “current” password.

Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (<http://ctep.cancer.gov>) or by calling the PMB at (240) 276-6575.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (<http://ctep.cancer.gov>) or by calling the PMB at (240) 276-6575.”

8.1 Ibrutinib (NSC 748645) PCI-32765

8.1.1 Chemical name: 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one

8.1.2 Classification Selective, irreversible, small molecule inhibitor of Bruton’s tyrosine kinase (BTK).

8.1.3 CAS Registry Number: 936563-96-1 M.W.: 440.5 g/mole

8.1.4 Mode of Action

Ibrutinib binds covalently to a cysteine residue in the BTK active site, leading to potent and irreversible inhibition of BTK enzymatic activity of B-cell receptors (BCR). B-cell maturation is mediated by BCR

- signal transduction and BTK is an essential part of the signaling pathway.
- 8.1.5 Description
White to off-white crystalline solid
- 8.1.6 Storage and Stability
Ibrutinib Hard Gelatin Capsules should be stored at 15 – 25°C. Shelf life surveillance of the intact bottles is ongoing.
- 8.1.7 Administration
Orally, with 8 ounces (approximately 240 ml) of water. The capsules are to be swallowed intact, not less than 30 minutes before or 2 hours after a meal. Patients should avoid consuming food and beverages containing grapefruit juice or Seville oranges for the duration of the study due to CYP3A4/5 inhibition. Doses are to be taken at about the same time each day. If an ibrutinib dose is missed, it should be made up as soon as possible on the same day with a return to the normal schedule the following day.
- 8.1.8 Preparation
Ibrutinib is supplied as hard gelatin capsules containing micronized Ibrutinib and the following excipients: microcrystalline cellulose; croscarmellose sodium; sodium lauryl sulfate; may contain magnesium stearate.
- 8.1.9 Availability / How supplied
Ibrutinib is supplied by Pharmacyclics, Inc., and distributed by the CTEP, DCTD, NCI. Capsules are packaged in 60-ml high-density polyethylene (HDPE) bottles with an induction seal and a child resistant screw top cap. Each bottle contains 92 capsules.
- 8.1.10 Dose Specifics
Arm A 420 mg PO, each day, days 1-28. Capsules are 140mg strength in a size 0, gray, hard gelatin capsule.
- 8.1.11 Side Effects
See CAEPR, Section [Error! Reference source not found.](#)
- 8.1.12 Potential Interactions
Ibrutinib is metabolized primarily by CYP3A4/5. Due to this potential increase in Ibrutinib exposure, concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A4/5 can increase ibrutinib exposure and should be avoided (see [Appendix VIII](#)). Patients should also be advised to avoid vitamin E and fish oils. Strong inducers of CYP3A4/5 should be avoided. A comprehensive list of inhibitors, inducers, and substrates may be found at <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>. This website is continually revised and should be checked frequently for updates. Alternative agents with mild or no CYP3A4/5 inhibition should be considered. Co-administration of ketoconazole, a strong CYP3A4/5 inhibitor, in 18 healthy subjects, increased dose normalized exposure

(C_{max} and AUC_{0-last}) of ibrutinib by 29- and 24-fold, respectively. Therefore, concomitant administration of ibrutinib with strong inhibitors of CYP3A4/5 (see [Appendix VIII](#)) should be avoided.

If a strong CYP3A4/5 inhibitor must be used, the Medical Monitor should be consulted before the use, and a dose reduction of ibrutinib to 140 mg daily or temporary hold of ibrutinib should be considered. Subjects should be closely monitored for potential treatment-related toxicities. If ibrutinib is temporarily held or the dose reduced due to administration of strong CYP3A4/5 inhibitors, patients may return to the previous dose of ibrutinib once they are no longer taking strong CYP3A4/5 inhibitors. Moderate CYP3A4/5 inhibitors (see [Appendix VIII](#)) should be used with caution. If the benefit outweighs the risk and a moderate CYP3A4/5 inhibitor must be used, reduce ibrutinib to 140 mg for the duration of the inhibitor use. No dose adjustment is required when ibrutinib is administered in combination with mild inhibitors. Grapefruit juices and Seville oranges may also increase ibrutinib plasma concentrations and should be avoided for the duration of ibrutinib treatment.

Warfarin and other vitamin K antagonists are not permitted in combination with ibrutinib. Patients should also be advised to avoid fish oil and vitamin E supplements while taking ibrutinib.

Although short term use (< 4 weeks) of pulse steroids are permitted, long term use of prednisone at a dose > 20 mg per day (or equivalent) is not permitted.

Supplements such as fish oil and vitamin E preparations should be avoided.

Patients with congenital bleeding diathesis have not been studied. For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries, see Section [5.4](#).

If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the patient is clinically stable and has no signs of bleeding. Patients should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted. See also Section [5.4.9](#).

In addition to the above considerations, any non-study protocol related chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the patient is receiving ibrutinib therapy.

Corticosteroids for the treatment of the underlying malignancy are prohibited.

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8.1.13 Overdose

Any dose of study drug administered in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in

the appropriate time frame and documented as clinical sequelae to an overdose.

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

8.2 Allopurinol (Lopurin, Zyloprim)

8.2.1 Availability

Commercially available as 100 mg and 300 mg tablets. Please refer to the agent's package insert for additional information.

8.2.2 Preparation

A 20 mg/mL suspension may be made by crushing eight 300 mg tablets and mixing with 120 mL of either 1:1 mixture of Ora-Sweet® and Ora-Plus® or a 1:1 mixture of Ora-Sweet®SF and Ora-Plus®. The resulting suspension is stable for 60 days refrigerated.

8.2.3 Storage & Stability

Store tablets in a tight container at 15°-30°C.

8.2.4 Administration

300 mg/day by mouth days 1 through 14 (total of 14 days) of cycles 1 and 2 unless allergic. See Section [5.1.1.3](#).

Administer by mouth. Fluid intake should be sufficient to yield a daily urine output of 2 liters.

8.2.5 Toxicity

Dermatologic toxicity, including pruritic maculopapular rash, urticaria, exfoliative dermatitis, and hemorrhagic dermatides which may be accompanied by alopecia, fever, and malaise. Stevens-Johnson syndrome (exfoliative dermatitis with mucous membrane involvement) has been reported. Patients with compromised renal function may be at a greater risk of development of rashes. Skin reactions may be delayed as long as two years after initiation of therapy. Gastrointestinal side effects, including nausea, diarrhea, and abdominal pain may occur. Drowsiness may also occur.

8.2.6 Drug Interactions

Concomitant usage of allopurinol and drugs that can increase serum urate concentrations, e.g., diuretics and alcohol, may necessitate an increase in allopurinol dosage. Administration of allopurinol with ampicillin or amoxicillin may increase the risk of skin rash. Allopurinol and chlorpropamide may result in an increased risk of hypoglycemia, whereas allopurinol with co-trimoxazole is associated with increased risk of thrombocytopenia.

8.3 Rituximab (IDEC-C2B8, Rituxan®)

8.3.1 Availability

Rituximab is commercially available in 10 mL and 50 mL single-use vials containing 100 mg or 500 mg rituximab solution, respectively, at a concentration of 10 mg/mL. Please refer to the agent's package insert for additional information.

8.3.2 Storage & Stability

Intact vials should be stored under refrigeration (2°-8°C). Dilute solutions for infusion (1-4 mg/mL) are stable for 24 hours under refrigeration, and for an additional 24 hours at room temperature.

8.3.3 Preparation

The desired dose of rituximab should be diluted in 0.9% NaCl or D₅W to a final concentration of 1-4 mg/mL. The solution should be mixed by gently inverting the bag.

8.3.4 Administration

Arm A:

Cycles 2 through 7

Rituximab, 50 mg/m² IV on day 1 of Cycle 2, and 325 mg/m² on day 2 of Cycle 2,

then 500 mg/m² on day 1 of Cycles 3-7.

Arm B

Cycles 1 through 6

Rituximab, 50 mg/m² IV on day 1 and 325 mg/m² on day 2 of Cycle 1 and 500 mg/m² on day 1 of Cycles 2-6.

8.3.5 Side Effects

Refer to package insert for rituximab for additional information.

Likely side effects include: Chills ,Fever ,Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing, Lowered white blood cell count, Less likely side effects include: Lowered red blood cell count (may cause anemia , weakness, fatigue) Fever associated with dangerously low levels of a type of white blood cell (neutrophils), Heart attack caused by a blockage of a blood vessel supplying part of the heart , Fast heartbeat, Belly pain, Diarrhea, Nausea or the urge to vomit, Vomiting, Swelling of the arms and/or legs, Fatigue or tiredness, Pain, Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing. Allergic reaction to other medications, injected proteins, or antisera (blood product) used to treat certain medical conditions (such as an infectious or poisonous substance), Infection, Awakening of viruses which have been latent/dormant, Infection in HIV positive patients, Lowered platelet

count that might interfere with clotting (may make you more likely to bruise or bleed), Decrease in the total number of white blood cells (leukocytes), Increased blood sugar level, Decreased blood level of calcium, Decreased blood level of potassium, Joint pain, Back pain, Muscle pain, Pain in the area of the tumor, Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness), Headache or head pain, Abnormal drowsiness or sluggishness, an unusual lack of energy, Convulsion or seizure, Sudden or traumatic injury to the kidney, Stuffy or runny nose, sneezing, Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath, Cough, Shortness of breath, Decrease in the oxygen supply to a tissue, Inflammation of the lungs that may cause difficulty breathing and can be life-threatening, Sore throat, Excess sweating, Itching, Skin rash, Swelling of body tissue underneath the skin, Hives, Sudden reddening of the face and/or neck, High blood pressure, Low blood pressure. Rare but serious side effects include: Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness. Group of signs and symptoms due to rapid breakdown of tumor that can occur after treatment of cancer has started that causes increased levels of blood potassium, uric acid, and phosphate, decreased levels of blood calcium, and kidney failure. Disease affecting brain tissue, caused by the JC virus. Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs. Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue. Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer). Life-threatening condition affecting greater than 30% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)

8.4 Fludarabine Monophosphate [Fludara; Berlex laboratories]

8.4.1 Availability

IV: Fludarabine monophosphate is commercially available as a sterile powder in 50 mg vials containing 50 mg of mannitol and sodium hydroxide to adjust the pH to 7.7. Please refer to the agent's package insert for additional information.

PO: An oral formulation of fludarabine will be used by Canadian institutions. Fludarabine is available in 10 mg tablets.

8.4.2 Storage & Stability

Intact vials should be stored under refrigeration (2°-8°C). Reconstituted fludarabine phosphate contains no antimicrobial preservative and thus should be used within 24 hours of reconstitution. Solutions diluted in D₅W or NS are stable for 48 hours at room temperature or under refrigeration.

- 8.4.3 Preparation
- IV:** Vials of fludarabine are reconstituted with 2 mL of sterile water for injection to yield a 25 mg/mL solution. The product should be further diluted for intravenous administration in 100 or 125 mL 5% dextrose or in 0.9% saline.
- 8.4.4 Administration
- Fludarabine 25 mg/m² IV days 1, 2, 3
- IV:** Fludarabine will be administered as an IV infusion over 30 minutes.
- 8.4.5 Toxicity
- Myelosuppression (dose limiting toxicity), fever, nausea and/or vomiting, skin rashes, myalgia, fatigue, autoimmune hemolytic anemia (may be life-threatening), and pulmonary toxicity (both pneumonia and pulmonary hypersensitivity reactions have been reported; fatal pulmonary toxicity has been described, especially when fludarabine was used in combination with pentostatin). Severe or fatal CNS toxicity presenting with loss of vision and progressive deterioration of mental status has been described primarily after high doses of fludarabine monophosphate, or at usual doses (25-30 mg/m²) in elderly patients. Very rarely described complications include transfusion-associated graft versus host disease, thrombotic thrombocytopenic purpura, and liver failure. Tumor lysis syndrome has been observed, especially in patients with advanced bulky disease. Opportunistic infections (protozoan, viral, fungal, and bacterial) have been observed. Please refer to the package insert for additional information. Please also see Section [8.5.6](#) for a list of possible side effects when used in combination with cyclophosphamide.
- 8.4.6 Drug Interactions
- Chronic use of corticosteroids with fludarabine should be avoided due to a significant increase in opportunistic infections.
- 8.5 Cyclophosphamide (Cytoxan[®]; CTX; CPA; Endoxan[®]; Neosar[®]; Cytoxan Lyophilized[®])
- 8.5.1 Availability
- Commercially available as a powder for injection in 100 mg, 200 mg, 500 mg, and 1 gram and 2 gram vials. Please refer to the agent's package insert for additional information.
- 8.5.2 Storage & Stability
- Intact vials should be stored at room temperature. Reconstituted and diluted solutions are stable for 24 hours at room temperature and 6 days if refrigerated.
- 8.5.3 Preparation
- Reconstitute 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials with 5, 10, 25, 50, or 100 mL of sterile water for injection or normal saline

to give a final concentration of 20 mg/mL. Vigorous shaking and/or gentle warming may be necessary for non-lyophilized preparations. Bacteriostatic water for injection (paraben preserved only) may be used; benzyl alcohol derivatives may NOT be used. Further dilute in D₅W or normal saline for IV infusion.

8.5.4 Administration

Cyclophosphamide 250 mg/m² IV, days 1, 2, 3

Administer by slow IV push or IV infusion over 30 minutes.

All patients should be adequately hydrated before and several days after each cycle of treatment. This is especially important to minimize hemorrhagic cystitis as well as the occurrence of tumor lysis syndrome in patients with bulky adenopathy or leukocytes > 50,000/μL.

8.5.5 Toxicity

Myelosuppression, hemorrhagic cystitis, syndrome of inappropriate antidiuretic hormone (SIADH), fatigue, hyperuricemia, azospermia, amenorrhea, cardiotoxicity (myocardial necrosis) with high doses.

8.5.6 Possible side effects, Fludarabine combined with Cyclophosphamide

Some of the Risks and Side Effects with Fludarabine and Cyclophosphamide are listed below (additional information can be found in the package insert):

Likely: Lowered white blood cell count (neutrophils/granulocytes) that may lead to infection, Lowered platelets which may lead to an increase in bruising or bleeding, Lowered red blood cells which may cause anemia, tiredness, or shortness of breath, Lowered number of another type of white blood cells (lymphocytes) that may lead to infection, Fatigue, Nausea, Vomiting, Time away from work, Hair loss, "Shingles." If you develop a condition known as shingles (Herpes zoster infection of the skin), a skin rash caused by the chicken pox virus, it will be important that you notify your physician immediately. There is a medication available to treat shingles effectively, but only if the medication is started within 24-48 hours after the rash has developed, Should these side effects occur, they can be treated with blood products (transfusions), antibiotics, and a reduction in the amount of chemotherapy given to you. Until your immune system has recovered from treatment, any blood products you may receive should be irradiated. Less Likely: Allergic reaction, Severe allergic reaction that causes fever, aches and pains in the joints, skin rash, and swollen lymph glands, Stuffy or runny nose, sneezing, Sore throat, Abnormal fast heartbeat, Excessive sweating, Flushing, Itching, Rash, Swelling of the lips, eyes, tongue, and throat which can be severe, Hives, Diarrhea, High blood sugar, Low blood potassium, Dizziness, Convulsion or seizure, Abdominal pain, Pain such as back, joint, and/or muscle pain, Headache, Wheezing, Cough, Shortness of breath, Inflammation of the lung which may cause difficulty breathing and difficulty getting oxygen, Infertility or sterility, Irregular menstrual periods. Some women may not resume their periods, Abnormal

production of a hormone that regulates salt and fluid excretion, Increased production of tears associated with the administration of cyclophosphamide, Metallic taste, Bladder irritation which may cause blood to appear in your urine. To minimize this side effect, patients are encouraged to drink fluids to promote frequent urination on the days of cyclophosphamide administration and one day afterwards. Rare But Serious: Destruction of red blood cells that may lead to anemia. Should this occur, it can be treated with blood transfusions, Changes in vision or changes in degree of alertness both of which can be severe or fatal, Rash which may become severe, Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the outer skin layer to separate from the middle layer, Life-threatening condition affecting greater than 30% of the skin in which cell death causes the outer layer of skin to separate from the middle layer, Severe lung dysfunction resulting in the ability to breathe which can be life-threatening, Allergic reactions to blood transfusions, Tumor lysis syndrome - a rapid decline in the number of tumor cells that can lead to kidney failure and/or chemical imbalances that may have a serious effect on other organs like your heart. If this were to occur, you would receive close monitoring and blood tests, as well as appropriate medical treatment, Liver problems/liver failure

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9. Statistical Considerations

9.1 Study Design and Objectives

This is a randomized phase III study designed to evaluate the ability of Ibrutinib-based induction therapy to improve the efficacy and tolerability of fludarabine-based chemoimmunotherapy for patients ≤ 70 years old with untreated symptomatic CLL. Five hundred and nineteen (519) patients will be randomized 2:1 to the Ibrutinib arm (A, 346 patients) and the FCR control arm (B, 173 patients).

The primary objective is to definitively evaluate whether patients who receive Ibrutinib-Rituximab have significantly longer PFS than those receiving FCR. With the planned sample size, we will have 80% power to detect a true hazard ratio of 1.5 (FCR vs. Ibrutinib) while controlling the one-sided type I error at 2.5%. Overall survival will be used as a secondary endpoint. If PFS is found to be significantly longer in the Ibrutinib-Rituximab arm than the FCR arm, with an additional 34 months of follow-up, we will have 80% power to detect a true hazard ratio of 1.67 (FCR vs Ibrutinib) in terms of OS while controlling the one-sided type I error at 2.5%.

Interim analyses will be performed. The study will be monitored for early stopping in favor of superior PFS in the experimental Ibrutinib arm, or for evidence of lack of benefit.

Because of the expected lower toxicity and non-curative nature of the Ibrutinib therapy, quality of life (QOL) is an important secondary study objective for this study. Questionnaires will be administered to learn the QOL impact of disease as well as treatment in this patient population. If both PFS and OS are found to be significantly longer in the Ibrutinib arm than in the FCR arm, QOL results will be considered for labeling in the EU.

Summaries of other secondary objectives of the study are listed below. Details can be found in the Objectives section of the protocol.

- Evaluate patient overall survival (OS);
- Monitor and assess toxicity;
- Determine the effect of pre-treatment characteristics on outcome;
- Determine if the minimal residual disease (MRD) status is an effective marker for prolonged PFS and OS;
- Explore changes in genetic abnormalities and intra-clonal architecture pre and post treatment and their relationship with treatment resistance.
- Explore the effects of therapy on immune function;
- Validate SNPs found to be associated with efficacy and toxicity of fludarabine-based therapy in the E2997 trial;
- Develop and evaluate a prognostic model to predict clinical outcome;
- Evaluate signaling networks downstream of the B-cell receptor in patients receiving Ibrutinib-based therapy.
- Study mechanisms of resistance to FCR and Ibrutinib-based therapy.

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9.2 Accrual

Based on previous studies conducted through the North American Intergroup collaboration (e.g. CALGB10404) in similar patient populations, we expect the annual accrual rate to be approximately 180 patients per year. It will take approximately 35 months to accrue the 519 patients for the study. Assuming median PFS for the Ibrutinib and FCR arms to be 78 and 52 months, respectively, the Ibrutinib vs. FCR comparison requires approximately 32 months of follow-up to reach full information of 203 events.

9.3 Primary Endpoint and Sample Size

The primary goal is to definitively evaluate whether patients who receive Ibrutinib-Rituximab have significantly longer progression-free survival (PFS) than those who do not. PFS is defined as the time from randomization to progression or to death without documentation of progression. We wish to have good power to detect a true hazard ratio of 1.5 (FCR vs. Ibrutinib-rituximab) controlling the one-sided type I error at 2.5%. Assuming PFS follows an exponential distribution, adjusted for sequential monitoring described below, a sample size of 519 patients randomized 2:1 to arms A (Ibrutinib-rituximab) and B (FCR) with 346 and 173 patients in the two arms, respectively will yield a nominal 80% power to detect a hazard ratio of 1.5 (median PFS of 52 vs. 78 months in FCR vs. Ibrutinib-rituximab) using a nominal one-sided $\alpha=0.025$ logrank test for the Ibrutinib-based regimen vs. FCR comparison. The required number of events for full information is 203.

A stratified logrank test applied to all patients as randomized will be the primary analysis, with age (< 60 years vs. \geq 60 years), ECOG performance status (0/1 vs. 2), disease stage (3/4 vs. 1/2), and baseline cytogenetic abnormalities (deletion of 11q22.3(ATM) vs. others) as stratification factors. The same analysis applied to eligible patients only will also be performed as a sensitivity analysis. Cox proportional hazards models will be used to assess possible effects of clinical and biological characteristics on outcome, including age, gender, disease stage, cytogenetic abnormalities, ECOG performance status, and important mutations. Treatment and covariate interactions will also be examined.

9.3.1 Since this is an unblinded trial, it is possible a difference in unscheduled CT scans could emerge between arms. All unscheduled CT scans performed on both arms as well as the reason for unscheduled CT scans will be recorded to identify differences in the frequency of unscheduled CT scans between arms (See Section [6.1.3.4](#)).

9.3.2 It is anticipated that most cases of disease progression will initially be identified by an objective increase in the absolute lymphocyte count (ALC) on CBC or simultaneous increase in ALC and progressive lymphadenopathy.

9.3.3 Given the unblinded nature of the trial however, it is possible that a difference in the interpretation of palpable lymphadenopathy could occur between arms. As detailed in Section [6.1.3.5](#), to address this possibility, we will record the pattern of relapse by classifying all patients experiencing progression as:

- Progression due to rising ALC only

- Progression determined by lymphadenopathy on physical exam only
- Progression due to both rising ALC and physical exam

These data will be used to evaluate the progression events on each arm of the study to assess whether there is a higher rate of progression by “physical exam only” in one study arm. Since we anticipate follow-up will be fairly mature before a large number of progression events occur on each arm, we will monitor differences in the pattern of progression at 6 month intervals from the outset of the trial and take action if the difference becomes larger than the greater of 10 patients or 20%. If this occurs, the research team will assess whether there needs to be changes to the criteria for progression for those patients in who progression is based solely on physical exam.

Collectively, these data will allow us to determine if there is an imbalance in progression based only on the findings of physical exam or a difference in the frequency of unscheduled CT scans and to detect potential bias in classification of disease progression on this basis.

9.4 Phase III Interim Analysis of the Primary Endpoint

We will perform the first interim analysis 24 to 27 months after full accrual. If the study has reached the planned full information (i.e. 203 PFS events) by this time, then the first analysis would be the only analysis. If the study is not at full information, then interim analyses will be performed annually until full information is reached. Under the current accrual rate of 18.3 per month and assumed hazard rates for the two arms, interim and final analyses are expected to occur at 53 and 63 months after study activation. The upper boundary for the first interim analysis is 2.807, corresponding to one-sided p-value of 0.0025. The upper boundary for the final analysis will be determined using the Lan-DeMets error spending function to preserve the overall type-I error rate. Upper boundaries at the planned analyses times are shown in Table 1. If the upper boundary is crossed at the interim analysis, there is sufficient evidence of efficacy to stop the study in favor of the alternative.

Table 1: The Interim PFS Efficacy Analyses for Ibrutinib-Rituximab vs. FCR

Time from Study Start (Months)	Information Time	Events Under H_1	Boundary
53-56	0.83*	170	2.807
63	1.00	203	1.963

* Actual information time at interim analysis may be less due to data collection and processing.

The study will also be monitored for early stopping for harm and inefficacy. At 25% information, the DSMC may consider stopping the study for harm if the lower 95% confidence bound for the hazard ratio (Ibrutinib/FCR) is above 1. Inefficacy monitoring is scheduled to start after approximately 49% of the full information becomes available with repeated analyses at each semi-annual DSMC meeting. Linear 20% Inefficacy Boundary (LIB20) proposed by Freidlin et al. (2010) will be used [8]. At each interim analysis, if the estimated hazard ratio is larger than the cut-off value given in the LIB20 boundary, the study would be

stopped early for lack of efficacy. In this study, the LIB20 boundary goes from 1 to 0.92 on the hazard ratio scale (from 0 to -0.08 on the log hazard ratio scale).

9.5 Secondary Objectives

Overall survival, defined as the time from randomization until death due to any cause, will be used as a secondary endpoint. Previous data showed that the time to 25% of FCR patients dying was 62.5 months [2]. Assuming an exponential survival distribution, with a total of 519 patients and adjusted for sequential monitoring described below, we will have 80% power to detect a true hazard ratio of 1.67 (FCR vs. Ibrutinib regimen) using a nominal one-sided $\alpha=0.025$ log-rank test. The required number of deaths for full information is 125. A hierarchical testing strategy will be used, in that the difference in OS between the two arms will be tested only if PFS for the Ibrutinib arm is significantly longer than that of the FCR arm, which gives us a one-sided family wise type I error rate of 2.5%.

We will perform the first interim analysis for OS at the final analysis time for PFS, expected at 63 months after study activation. To preserve the overall type I error rate, critical values at the interim efficacy analyses will be determined using a truncated version of the Lan-DeMets error spending rate function corresponding to the O'Brien-Fleming (O-F) boundary. The upper O-F boundaries at the planned analyses times are shown in Table 2. If the upper O-F boundary is crossed at an interim analysis, that would be sufficient evidence of efficacy in favor of the alternative.

Table 2: The Interim OS Efficacy Analyses for Ibrutinib-Rituximab vs. FCR

Time from Study Start (Months)	Information Time	Events Under H_1	Truncated O-F Boundary
63	0.62	78	2.61
80	0.82	103	2.27
97	1.00	126	2.04

A stratified logrank test applied to all patients as randomized will be the primary analysis for OS, with age (< 60 years vs. \geq 60 years), ECOG performance status (0/1 vs. 2), disease stage (3/4 vs. 1/2), and baseline cytogenetic abnormalities (deletion of 11q22.3(ATM) vs. others) as stratification factors. The same analysis applied to eligible patients only will also be performed as a sensitivity analysis. Cox proportional hazards models will be used to assess possible effects of clinical and biological characteristics on outcome, including age, gender, disease stage, cytogenetic abnormalities, ECOG performance status, and important mutations. Treatment and covariate interactions will also be examined.

As per NCI CTCAE Version 4.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either "unrelated or unlikely to be related" to study treatment in the event of an actual relationship developing.

9.6 Quality of LifePrimary Endpoint

Quality of life (QOL) will be assessed using FACT-G and the leukemia subscale. The primary objective of the QOL study is to compare treatment toxicity-related QOL in patients receiving the experimental Ibrutinib-based therapy to those receiving standard FCR. The primary interest is the FACT-Leu Trial Outcome Index (TOI), which is comprised of the physical well-being (PWB) and functional well-being (FWB) components of the FACT-G and the leukemia subscale. The FACT-Leu TOI contains a total of 31 items, with scores ranging from 0 to 124. The 31-item FACT-Leu instrument will be administered at the following time points: at the time of randomization, three months and six months after randomization, at the 12 month response evaluation, and every six months thereafter for two years. The primary endpoint is the change in FACT-Leu TOI score from the time of randomization to 12 months after beginning therapy between the FCR arm and the Ibrutinib arm. An analysis of the cases with both baseline and month 12 evaluations by randomized treatment group will be performed as the primary analysis. If both PFS and OS are found to be significantly longer in the Ibrutinib arm than in the FCR arm, results from this analysis will be considered for labeling in the EU.

The FACT-Leu TOI is reported to have a standard deviation (SD) ranging from 18.1 to 21.7. Assuming 90% 1-year survival, correlation of 0.4 or 0.6 between FACT-Leu TOI scores at randomization and 1 year after beginning therapy, and compliance rates (proportion of patients alive at one year who complete the baseline and 1-year QOL assessments) of 50%, 65% and 80%, the difference in FACT-Leu TOI mean change score between the Ibrutinib arm and the FCR arm we can detect with 80% power at two-sided significance level of 0.05 ranges from 4.9 to 9.4, and are shown in Table 3.

Table 3. Differences in FACT-Leu TOI mean change scores

Standard deviation (SD)	Correlation	SD of change	Difference detected 50% compliance n ₁ =156, n ₂ =78	Difference detected 65% compliance n ₁ =202, n ₂ =101	Difference detected 80% compliance n ₁ =250, n ₂ =125
18.0	0.4	19.7	7.7	6.7	6.0
18.0	0.6	16.1	6.3	5.5	4.9
20.0	0.4	21.9	8.5	7.5	6.7
20.0	0.6	17.9	7.0	6.1	5.5
22.0	0.4	24.1	9.4	8.2	7.4
22.0	0.6	19.7	7.7	6.7	6.0

Secondary Endpoints

The change in FACT-Leu TOI score from the time of randomization to 3 months after beginning therapy will be compared between arm A and arm B to assess the short-term effect of the two therapies on QOL.

The change in FACT-Leu TOI score from the time of randomization to 6 months after beginning therapy will be compared between the two treatment arms in order to provide additional information regarding the toxicity of the different regimens.

Repeated measures analysis techniques, which use data from all time points will be utilized to examine the treatment effect and time effect on FACT-Leu TOI score. Methods described in Schluchter [3] and Schluchter, Greene and Beck [4] will be used, which account for the possibility of informative missingness by jointly modeling the longitudinal QOL score and the time to dropout.

In addition, the social well-being and emotional well-being components of the FACT-G will be administered at study entry. The entire FACT-Leukemia instrument (FACT-G and the leukemia subscale) at baseline will be analyzed using descriptive statistics to assess the impact of CLL on QOL independent of treatment.

The Morisky Adherence Scale will be used to measure the likelihood that a patient will take prescribed medications for patients on the Ibrutinib arm, at 3, 6, 12 and 24 months after beginning therapy. Descriptive statistics will be used to summarize trend in adherence to prescription.

9.7 Correlative Studies

We will determine the effect of pre-treatment clinical and biological characteristics on clinical outcomes in terms of CR rates and PFS. Baseline characteristics of interest include disease stage and IGHV mutation status. We will also genotype a number of SNPs investigated in a previous ECOG trial E2997, which explored the association of these SNPs with the efficacy and toxicity of fludarabine-based therapy.

CR rates will be estimated within marker-defined subgroups. A marker will be dichotomized at the median if it takes continuous values. The difference in CR rates between subgroups will be estimated with 95% confidence intervals. If subgroups are of equal size, assuming a 50% overall CR rate, we have 80% power to detect a difference of 12.5% (56.2% vs. 43.7%) in CR rates between the subgroups with two-sided type I error rate of 0.05, if we have marker measurements for all 519 patients. If 80% of the patients (415 patients) have marker measurements, the difference we can detect is 14.2% (57.1% vs. 42.9%). A multivariate logistic regression model will be used to assess the effects of markers and clinical covariates on CR rates jointly.

PFS will be estimated within marker-defined subgroups with the Kaplan-Meier method, and 95% confidence intervals will be calculated at different time points. With a total of 519 patients and 203 events, we have 80% power to detect a hazard ratio of 1.49 between the subgroups with two-sided type I error rate of 0.05, assuming the two subgroups are of equal size. If 80% of the patients have marker measurements, the hazard ratio we can detect is 1.56, assuming the proportions of patients missing marker measurements are the same between events and censored cases. A multivariate Cox proportional hazards model will be used to assess marker and clinical covariate effects on PFS jointly.

MRD will be assessed by flow cytometry at the 12 month response evaluation in patients on both treatment arms as well as longitudinally in the Ibrutinib arm. The proportion of patients with an MRD negative remission at the time of the 12 month response evaluation will be compared across arms using two-sample binomial tests. Pair-wise comparisons of MRD levels at different time points within a given treatment arm will be made using the Wilcoxon signed-rank test to determine when MRD levels nadir for most patients.

We will use the landmark method [5] to assess the association between a particular MRD status time-point and outcome (PFS and OS). For each time point, only patients without a prior event and evaluated at that time will be included. Assuming that i) time to 25% patients dying is 62.5 months, ii) 90% patients have MRD measurements, and iii) the percentage of patients achieving MRD- status, being 60% for the FCR arm and 25% for the Ibrutinib arm, the hazard ratios in terms of PFS we can detect after 32 months of follow-up with 80% power and a two-sided type I error of 0.05 are 0.52, and 0.48, respectively, for the FCR arm and Ibrutinib arm. The MRD time point that is the most predictive of outcome is the one that gives the largest log-rank statistic by the landmark method. The performance of this predictor can be assessed by a cross-validation scheme, as described in Simon et al [1]. Cross-validated Kaplan-Meier curves will also be constructed and their significance computed by permutation. We will investigate whether a different threshold to classify MRD status at a given time-point provides a more accurate prediction of PFS using the same cross-validation strategy. Cross-validated ROC curves as well as the C-statistics will be used to summarize the performance of the predictors.

A joint longitudinal analysis of MRD levels will also be performed using random effects models described in Schluchter and Schluchter, Greene and Beck [3,4]. These account for informed missingness to assess treatment differences in the rate of change in the longitudinal analysis of MRD levels. The association of outcome (PFS) with MRD levels at the relevant time points will be explored using Andersen-Gill type of model with time-dependent covariates [7]. Similar modeling with relapse free survival as the outcome will be explored to understand how rising MRD levels post therapy predict relapse. Cross-validation will be used to evaluate prediction accuracy.

Effects of FCR and Ibrutinib-based therapy on T-cell immune function will be explored. We will measure T-cell counts and assess area of immune synapse at 12 months. Histograms of these counts will be plotted by arm. Medians will be compared using the Wilcoxon rank sum test. We will also measure T-cell immune repertoire, which will be explored using descriptive statistics.

As an exploratory analysis, the immune system will also be evaluated by Pneumococcal vaccination, administered to the first 100 patients on each arm who have not previously received the Prevnar 13 vaccination at the 12-month response evaluation. Opsonophagocytic activity (OPA) titers against 6 pneumococcal serotypes will be measured pre-vaccination and on day 90 post vaccination. Overall Prevnar response (OPR) is defined as a 4-fold rise or more in geometric mean antibody titers for at least 4 of the 6 serotypes. Assuming an overall OPR rate of approximately 25% for the two arms, we have 80% power to detect a difference of 16% (FCR) vs. 34% (Ibrutinib) or more with a one-sided significance level of 0.025 using a two-sample binomial test. OPR rates will be estimated for the two arms with 95% confidence intervals.

We will build and evaluate a prognostic model that incorporates clinical and biological characteristics to predict response to therapy and clinical outcome. A 5-fold cross-validation scheme will be used. Patients will be randomly divided into five parts, four of which used for training and the remaining part used for testing. During the training stage, we will select important variables based on their p-values in Cox-proportional hazards models. A risk score and a classification rule can be developed from these variables. In the testing stage, the risk score is

computed for patients in the test set and used to predict their clinical outcome. Similarly, patients in the test set can also be classified to be responders or non-responders based on the classification rule. This process of training and testing can be repeated many times. The performance of the risk score and the classification rule can be evaluated using C-statistics and ROC curves.

Baseline and relapse samples will be collected to allow exploratory sequencing of Bruton's tyrosine kinase and downstream targets to study mechanisms of resistance to both FCR and Ibrutinib-based therapy. We will examine change across time from baseline to progression and explore clonal evolution, and epigenetic changes in methylation. Descriptive statistics will be used to find genes that play important roles in drug resistance.

9.8 Anticipated Accrual by Gender and Ethnicity

Based on previous data from E2997 the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	Gender		
	Females	Males	Total
Hispanic or Latino	2	5	7
Not Hispanic or Latino	151	361	512
Ethnic Category: Total of all subjects	153	366	519
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	7	7
Black or African American	17	48	65
Native Hawaiian or other Pacific Islander	0	0	0
White	136	311	447
Racial Category: Total of all subjects	153	366	519

9.9 Randomization Procedure

Patients will be randomized 2:1 to the Ibrutinib arm (A) and the FCR control arm (B) using permuted blocks with stratification and dynamic balancing on main institutions [6]. The stratification factors are age (<60 vs. ≥ 60), ECOG performance status (0/1 vs. 2), disease stage (3/4 vs. 1/2), and baseline cytogenetic abnormalities (deletion 11q22.3 (ATM) vs. other).

9.10 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or

blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Center.

9.11 Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required.

References for Statistical Section:

1. Simon RM, Subramanian J, LI MC, Menezes S. Using cross-validation to evaluate predictive accuracy of survival risk classifiers based on high-dimensional data. *Brief Bioinform* 2011; 12(3): 203–214.
2. Hallek M, Fischer K, Fingerle-Rowson G, et al. (2010) Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*; 376(9747):1164-1174.
3. Schluchter MD (1992) Methods for the analysis of informatively censored longitudinal data. *Statistics in Medicine*; 11, 1861-1870.
4. Schluchter MD, Greene T and Beck GJ (2001) Analysis of change in the presence of informative censoring application to a longitudinal clinical trial of progressive renal disease. *Statistics in Medicine*; 20:989-1007.
5. Anderson JR, Cain KC, Gelber RD (1983) Analysis of survival by tumor response. *J Clin Oncol*. 1983;1:710-719.
6. Zelen M (1974) The randomization and stratification of patients to clinical trials. *Journal of Chronic Diseases*, 27:365-375.
7. Andersen PK & Gill RD. Cox's regression model for counting processes: a large sample study. *The annals of statistics*, 1982; 10(4), 1100-1120.
8. Freidlin, B., Korn, E. L., & Gray, R. (2010). A general inefficacy interim monitoring rule for randomized clinical trials. *Clinical Trials*, 7(3), 197-208.

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10. Correlative Studies

- NOTE:** ECOG-ACRIN requires that all biological samples submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System. An STS shipping manifest form must be generated and shipped with the sample submissions. See Section [10.4](#).
- NOTE:** Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG-ACRIN Operations Office – Boston regarding logistics for submission of fresh samples.
- NOTE:** Please note there are sample submissions to **two** separate laboratories outlined in Sections [10.1](#) and [10.2](#).
- NOTE:** Patients must sign informed consent before the submission of the samples. If submitting baseline samples prior to patient enrollment to the trial, please use the Generic Specimen Submission Form (#2981) and call the receiving laboratories prior to shipping. Once the patient is randomized please call the receiving laboratories with the ECOG-ACRIN patient sequence number and retroactively log the sample information into the ECOG-ACRIN Sample Tracking System.

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10.1 Submissions to the ECOG-ACRIN Leukemia Translational Research Laboratory

Derivatives from peripheral blood or bone marrow from patients entered on studies of hematologic malignancies are stored in ECOG-ACRIN's Leukemia Tissue Bank for future laboratory studies. The bank provides the scientific community a source of leukemia specimens that are collected, processed, and maintained following quality control and quality assurance guidelines. The bank will accommodate requests from investigators within and outside ECOG-ACRIN in a timely and efficient manner, with respect to tissue type, tissue preparation, and most importantly, biologic characteristics of specimens.

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10.1.1 Sample Collection and Submission Schedule

NOTE: All cooperative groups should send specimens to the ECOG-ACRIN Leukemia Translational Research Laboratory.

All samples should be clearly labeled with the ECOG-ACRIN protocol number E1912, the patient's initials, ECOG-ACRIN patient sequence number (if available), date of collection, and type of sample (PB or BM).

- Bone marrow biopsy smears must be submitted at baseline for central review.
- Bone marrow sections/slides must be submitted at baseline and at the time of the twelve (12) month response evaluation for central histological review.

NOTE: Submission of pathology samples for central review is mandatory in order for the patient to be considered evaluable. Failure to submit pathology samples may render the case unevaluable.

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NOTE: Bone marrow biopsy sections/slides are distinct from bone marrow smears.

- Peripheral blood and buccal cells should be submitted at baseline for banking per patient consent.

NOTE: Dr. Paietta’s institutional regulations require that she receive copies of patient consents and HIPAA authorization forms along with the baseline samples.

If you have any questions, please contact the LTRL at (718) 920-4100.

Biological Materials	Baseline ¹	Twelve (12) Month Response Evaluation (52 weeks after day 1 of cycle 1)
MANDATORY for Central Review		
Bone Marrow Biopsy Sections/Slides ⁴	X	X
Bone Marrow Smears (Wright-Giemsa stained)	X	
From Patients Who Answer “YES” to “I agree to provide additional specimens for research.”		
Peripheral Blood (serum, (2) 10mL red top tubes, 15-20mL)	X	
Peripheral Blood (heparin, (4) 10mL green or purple [EDTA] top tubes, 30-40mL)	X	
Buccal Rinse (preferred) or Swab ³	X	

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- Submit after randomization, prior to treatment.
- [Deleted in Addendum #2]
- Buccal rinse (preferred) or swabs are strongly encouraged to be collected prior to the start of treatment, but can be collected at any other time during the study, if necessary.
- Baseline bone marrow biopsy sections/slides should be submitted within one (1) month of randomization.

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10.1.2 Sample Preparation Guidelines

The following samples **must** be submitted:

Bone Marrow Smears

- At least two (2) Wright-Giemsa stained bone marrow smears

Bone Marrow Biopsy Sections/Slides

- Submit eight (8) unstained slides cut at five (5) microns. Label the slides with the ECOG-ACRIN patient sequence number, date of collection, and order of sections. Do not bake or place cover slips on the slides.

NOTE: Bone marrow biopsy sections/slides can be from the clinical biopsy performed within three (≤ 3) months prior to registration if the on-study baseline bone marrow biopsy was not performed.

NOTE: **Bone marrow biopsy sections/slides are distinct from bone marrow smears.**

A copy of the institutional pathology report on the bone marrow must be submitted via Medidata Rave. The pathology report must include cytogenetic results and any results from fluorescence-in-situ (FISH) hybridization and/or molecular studies done at the submitting institution. These documents are to be submitted via Medidata Rave. If Rave is unavailable please fax to the LTRL at (718) 920.1161.

10.1.2.1 The following should be submitted at baseline to be banked for use in future research studies:

- Two (2) 10mL red top serum tubes of peripheral blood (15-20mL)
- Heparinized or EDTA peripheral blood ([4] 10mL green or purple top tubes, 30-40mL)
- Buccal rinse (preferred) or swabs

NOTE: If samples designated for banking only are not submitted, please note the reason in the Comments section of the Sample Tracking System.

Buccal Cell Samples

- Most commonly, institutions will have buccal swab kits for the collection of cells for HLA-typing. Alternatively, Scope, a commercial brand mouthwash, or normal saline in a small sealed bottle can be given to the patient for a mouthwash
- Aseptic techniques must be used to collect buccal cells from patients on-site and buccal cells must not be contaminated with cells from any other source. Patients should not brush their teeth or consume food prior to buccal cell collection.
- If a cytobrush is used, the collection end should not be touched and the patient should not scrape his/her cheek too vigorously. The inside of the cheek should be scraped 6 times. Several models of cytobrushes are available, such as the Omni swab or Bio-Swab from Arrowhead Forensics or the Cyto-Pak CytoSoft Brush from Medical Packaging Corp.
- If mouthwash (e.g. Scope) or normal saline is used, the patient should pour approximately 10cc of mouthwash or saline into his/her mouth and vigorously swish it against the cheeks for 10 seconds and deliver the solution into a labeled 15cc polypropylene test tube. Among mouthwashes, the Scope brand fares best in collecting buccal cells for the preparation of high-quality DNA in high yield.

It is important that buccal cells do not dry out during shipping. Institutions are advised to seal the container containing the buccal cells tightly. Ship containers on ice-packs, together with the patient's peripheral blood.

10.1.3 Shipping Procedures

Log the shipment into the ECOG-ACRIN STS the day of shipment. If the STS is unavailable, a Generic Specimen Submission Form (#2981) must be submitted with the samples. Once STS is available, retroactively log the shipment into STS, using the actual collection and shipping dates.

The LTRL must be notified by telephone the day of shipment.

Fax or E-mail to Dr. Paietta is not acceptable.

Telephone: (718) 920-4100

During off hours, all information regarding the shipment should be left on the answering machine in the LTRL including:

E1912 Sequence Number

Patient's Initials

Type of Specimen Shipped

Name, Telephone Number, and Institution

Follow the directions given in the phone message.

For questions regarding the shipment, Dr. Paietta and her staff can be reached at the cell phone numbers provided on the recorded message. Please always try Dr. Paietta first. Questions can also be addressed to Dr. Paietta via e-mail (epaietta@earthlink.net), however, please do not use e-mail for shipment notifications.

The pre-trial diagnostic bone marrow biopsy slides/sections are to be submitted after randomization to the trial. On-study bone marrow slides are to be submitted within one month of randomization.

Peripheral blood, serum and buccal cells must be sent fresh (on the day of collection) on cool packs (do not freeze and do not use ice cubes) by overnight courier (preferably Federal Express) to arrive within 24 hours to:

Elisabeth Paietta, Ph.D.
Department of Oncology
Hofheimer 3rd Floor
Leukemia Oncology Laboratory
111 East 210th Street
Bronx, NY 10467
Tel: (718) 920-4100
FAX: (718) 920-1161
E-mail: epaietta@earthlink.net

An STS shipping manifest form must be generated and shipped with all sample submissions.

Please enter all information into the STS, including time and date of specimen collection and peripheral blood WBC count and blast count.

The LTRL is open to receive shipments Monday through Saturday. Shipments on Fridays for Saturday delivery must have "Saturday

Delivery” marked on the overnight courier slip. Also, please label the package with a handwritten note that says: Deliver to Hospital Main Lobby/Security.

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If samples need to be drawn late at night, on Sunday, or on a holiday when Federal Express does not operate, keep the samples in a refrigerator between 10 and 15 degrees Celsius until the next day when it can be shipped.

10.1.3.1 Sample Processing and Routing

Bone marrow biopsy sections/slides will be forwarded to Dr. Curtis Hanson at Mayo Clinic for central histological review.

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10.2 Submissions to Mayo Clinic for Correlative Studies

All samples should be clearly labeled with the ECOG-ACRIN protocol number E1912, the patient’s initials (last name, first name), ECOG-ACRIN patient sequence number (if available), and date of collection.

Kits are available to order, and will include materials necessary for the preparation and shipment of samples. Kits should be ordered at least 24 hours in advance of each sample time point. To order kits e-mail Kim Henderson at Henderson.Kimberly@mayo.edu. Please include the following information: site name, mailing address, contact person and number of kits requested.

Any questions concerning sample collection and shipment can be directed to Kim Henderson at (507) 284-3805.

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10.2.1 Sample Collection and Submission Schedule

Peripheral blood samples are requested at the intervals indicated below.

Biological Materials	Baseline ¹	After Three (3) Cycles of Therapy	After Six (6) Cycles of Therapy [Prior to Cycle Seven (7) Arm A, End of Cycle Six (6) Arm B]	Twelve (12) Month Response Evaluation (52 weeks after day 1 of cycle 1)	15, 18, 24, and 36 Months After Randomization	Time of Disease Progression or Relapse
From Patients Who Answer “YES” to “I agree to participate in the laboratory research studies that are being done as part of this clinical trial.”						
Peripheral Blood (sodium heparin (5) 10mL green top tubes)	X	X	X	X	X	X
Peripheral Blood (serum, (2) 10mL red top tubes)	X			X	X ²	

1. After randomization, prior to treatment.
2. Month 15 only.

NOTE: For patients who consent to the correlative studies, please submit ALL sequential blood samples at ALL time points.

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10.2.2 Shipping Procedures

Log the shipment into the ECOG-ACRIN STS the day of shipment. If the STS is unavailable, a Generic Specimen Submission Form (#2981) must be submitted with the samples along with the Patient Information Form, [Appendix I](#). Once STS is available, retroactively log the shipment into STS, using the actual collection and shipping dates.

Please include CBC and differential information (WBC and % lymphocytes) with each blood sample, if available, via the Sample Tracking System.

If your shipment was not logged into the ECOG-ACRIN STS please call Kim Henderson at (507) 284-3805 or e-mail Henderson.Kimberly@mayo.edu to notify the laboratory when samples are being shipped. Indicate the ECOG-ACRIN protocol number, the FedEx tracking number, and name and phone number of the contact person.

Place filled tubes in a styrofoam container with absorbent material and put in corrugated mailer box. Follow the packing guidelines listed in the kit. If samples are sent late in the week and will arrive on the weekend, please note "Saturday Delivery" on the Federal Express form.

Peripheral blood samples should be sent fresh, the day of collection, ambient and shipped overnight to arrive during normal working hours. The samples from multiple patients may be shipped together, but must be placed in separately labeled tubes and bags.

Ship Monday – Thursday only. The laboratory is open to receive shipments Monday through Friday.

FRIDAY AND PREHOLIDAY SHIPMENTS SHOULD BE AVOIDED

Packing instructions:

1. Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
2. Place the filled specimen bag in the Styrofoam container.
3. Loosely pack with paper toweling.
4. Place the Styrofoam container and the Sample Tracking System shipping manifest form within the cardboard mailing sleeve.
5. Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx air bill and adhere to the exterior lid of the box. Ship specimens via priority overnight delivery (next day delivery by 10am) the same day collected.
6. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

The blood samples in prepared kits should be shipped to the following address:

Kim Henderson
Mayo Clinic CLL Laboratory
613 Stabile
200 First Street, SW
Rochester, MN 55905

An STS shipping manifest form must be generated and shipped with all sample submissions.

Blood samples will be forwarded to Dr. Curtis Hanson at Mayo Clinic for analysis as described in Section [10.3](#).

10.3 Studies to be performed:

10.3.1 IGHV Mutation Analysis

The IGHV mutation status will be assessed at baseline to allow exploration of how IGHV mutation status correlates with clinical outcomes (CR, PFS) of the different treatment arms.

10.3.2 Minimal Residual Disease Assessment by Flow Cytometry

MRD status will be assessed in patients on both treatment arms at the time of the 12 month response evaluation (52 weeks after day 1 of cycle 1) to determine the ability of this conventional MRD time-point to predict clinical outcome (PFS, OS). Blood samples for MRD assessment by flow cytometry will also be collected on both treatment arms 24 and 36 months from randomization. An early MRD assessment is also planned at 3 months in the FCR arm of the study. Although samples will be collected and archived from all time-points in patients on both treatment arms, the initial planned MRD assessments at these other time-points will be tailored to address hypotheses specific to each arm. The initial planned time-points of assessment are:

MRD assessment time-points	3 mo	12 mo	24 mo	36 mo
FCR (Arm B)	X	X	X	X
Ibrutinib/rituximab (Arm A)		X	X	X

As noted, this plan will include assessment of MRD status after the first 3 cycles of FCR in arm B to confirm studies suggesting that ~25% of patients achieve an MRD negative disease state after 3 cycles of FCR.

Although a sample to permit MRD assessment at that time-point will also be collected for patients on the Ibrutinib arm, it is expected nearly all patients treated with Ibrutinib/rituximab have overt residual disease after only 3 months of therapy. Collectively, these longitudinal studies of MRD on both treatment arms will allow better characterization of when MRD levels nadir and help define the optimal timing of MRD assessment for both treatment approaches.

- 10.3.3 Genetic Studies:
DNA (germline and tumor cell) will also be collected at baseline and longitudinally to evaluate the association of genetic mutations in leukemic cells (clonal or sub-clonal) at baseline and during treatment with subsequent response to treatment using CIT and non-CIT approaches.
- 10.3.4 B-cell Receptor Signaling:
Blood cells will be collected at baseline and during treatment to evaluate signaling networks downstream of the B-cell receptor to help better define the mechanism of action (and potential mechanisms of resistance) to Ibrutinib based therapy.
- 10.3.5 Pharmacogenetics Studies:
DNA (germline) will also be collected at baseline to allow confirmatory genotyping of single nucleotide polymorphism associated with the efficacy and toxicity of fludarabine-based therapy in a prior ECOG GWAS analysis. DNA (both tumor and germline) will also be collected for exploratory GWAS studies to identify genetic characteristics associated with the efficacy and toxicity of sensitivity to Ibrutinib based therapy.
- 10.3.6 Thymidine Kinase:
Serum samples will be collected to allow assessment of baseline Thymidine Kinase levels.
- 10.3.7 T-Cell Studies:
Blood samples will be collected after 3 cycles of therapy, after 6 cycles of therapy, at the time of the twelve (12) month response evaluation, and during later follow-up to assess immune function including assessment of quantitative T-cell counts, T-cell repertoire, and T-cell function (immune synapse). Serum and plasma will also be collected at these time points to allow evaluation of immune cytokines.
- 10.3.8 Drug Resistance: Leukemia samples at the time of relapse or progression will be collected to allow biologic studies exploring the mechanisms of resistance to both fludarabine and Ibrutinib based therapy
- 10.3.9 As an exploratory endpoint, we will also evaluate specific immune response to Prevnar vaccination in a subset of patients on each treatment arm who have not previously received the Prevnar 13 vaccination: To allow functional evaluation of the immune system for patients on both arms, we will also measure the response of a subset of ~100 patients on each arm to pneumococcal vaccination (administered at the 12 month response evaluation) after both ibrutinib and FCR therapy. These critical studies go beyond describing changes in T-cell repertoire and synapse and actually evaluate the ability of the patient to respond to an immunologic challenge in vivo. We propose to perform studies below on the first 100 patients on each arm.

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Immunity following pneumococcal disease is directed primarily against the capsular polysaccharide of the bacteria serotype involved. Antibody mediated killing of *Streptococcus pneumoniae* by phagocytes is an important mechanism of protection. The two most common serologic methods for quantifying and evaluating the function of antibodies induced by pneumococcal vaccination are IgG quantification by enzyme-linked immunosorbent assay (ELISA) and measurement of opsonophagocytic activity (OPA) of antibodies from sera of vaccinated individuals. The OPA assay is a functional antibody assay that is important for the evaluation of candidate vaccines and is a requirement for the licensure of new pneumococcal conjugate vaccine formulations. OPA reflects in vivo mechanisms of defense against pneumococcal infection. The measurement of functional antibodies has been shown to better correlate with protection in infant populations and it is also likely to be a better indicator for elderly populations than the measurement of antibodies specific to the capsular polysaccharides by ELISA assay (Clin Infect Dis 47:1328). While there is no defined correlate of protection for pneumococcal vaccines, it is thought that OPA titers are associated with protection against invasive pneumococcal disease. The primary endpoint for Prevnar 13 adult clinical trials that led to the FDA approval of Prevnar 13 relied on immunogenicity endpoints of OPA geometric mean ratio (GMT) and proportion achieving at least 4-fold increase in OPA titer (MMWR Morb Mortal Wkly Rep. 61:394-395).

- Exploratory outcome for vaccine immunogenicity: OPA titers against 6 pneumococcal serotypes (1, 3, 5, 6A, 7F, 19A) included PCV13 vaccine at 90 days (15 month post registration sample) after immunization (fold change from pre-vaccination baseline sera responses).
- We will report pre-vaccination and day 90 post-vaccination (15 month post registration sample) OPA GMT titers for each serotype (1, 3, 5, 6A, 7F, 19A) in vaccine group and vaccine group + Lenalidomide.
- Overall Prevnar response will be defined as 4-fold rise in GMT for ≥ 4 of the 6 serotypes measured at 90 days post-vaccination.

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10.4 ECOG-ACRIN Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking <https://webapps.ecog.org/Tst>

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link:

<http://www.ecog.org/general/stsinfo.html> Please take a moment to familiarize yourself with the software prior to using the system.

A shipping manifest form must be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

Study Specific Notes

The Generic Specimen Submission Form (#2981) will be required only if STS is unavailable at time of sample submission, along with the Patient Information Form ([Appendix I](#) – to Mayo Clinic only). Indicate the appropriate Lab ID# on the submission form:

- 0002 = ECOG-ACRIN Leukemia Translational Research Laboratory
- 0156 = Mayo Clinic Hematology Research Laboratory

Retroactively enter all specimen collection and shipping information when STS is available.

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10.5 Banking

The residuals and/or derivatives of specimens collected for this study will be retained at the ECOG-ACRIN Leukemia Translational Research Laboratory/ECOG-ACRIN Leukemia Tissue Bank for possible use in ECOG-ACRIN approved future studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

10.6 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used will be submitted electronically via secure web application to the ECOG-ACRIN Operations Office – Boston on a monthly basis or upon request by any laboratory holding and/or using any specimens associated with this study.

10.7 Lab Data Transfer Guidelines

The data collected or generated on the above mentioned correlative studies will be submitted electronically via secure data portal to the ECOG-ACRIN Operations Office – Boston by the central laboratory on a quarterly basis.

11. Records to Be Kept

Please refer to the **E1912** Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

11.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

12. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

13. References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA: a cancer journal for clinicians*. 2011;61(2):69-90. Prepublished on 2011/02/08 as DOI 10.3322/caac.20107.
2. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008;111(12):5446-5456.
3. Shanafelt TD, Rabe KG, Kay NE, et al. Age at diagnosis and the utility of prognostic testing in patients with chronic lymphocytic leukemia. *Cancer*. 2010.
4. Call T, Phylly R, Noel P, et al. Incidence of chronic lymphocytic leukemia in Olmsted County, Minnesota, 1935 through 1989, with emphasis on changes in initial stage at diagnosis. *Mayo Clinic Proceedings*. 1994;69:323-328.
5. Catovsky D, Fooks J, Richards S. Prognostic factors in chronic lymphocytic leukaemia: the importance of age, sex and response to treatment in survival. *Br J Haematol*. 1989;72:141-149.
6. Dighiero G, Maloum K, Desablens B, et al. Chlorambucil in indolent chronic lymphocytic leukemia. *Frech Cooperative Group on Chronic Lymphocytic Leukemia*. *N Engl J Med*. 1998;338:1506-1514.
7. Diehl LF, Karnell LH, Menck HR. The American College of Surgeons Commission on Cancer and the American Cancer Society. The National Cancer Data Base report on age, gender, treatment, and outcomes of patients with chronic lymphocytic leukemia. *Cancer*. 1999;86(12):2684-2692.
8. Molica S, Levato D, Dattilo A. Natural history of early chronic lymphocytic leukemia. A single institution study with emphasis on the impact of disease-progression on overall survival. *Haematologica*. 1999;84(12):1094-1099.
9. Molica S, Levato D. What is changing in the natural history of chronic lymphocytic leukemia. *Haematologica*. 2001;86:8-12.
10. Flinn IW, Neuberg DS, Grever MR, et al. Phase III trial of fludarabine plus cyclophosphamide compared with fludarabine for patients with previously untreated chronic lymphocytic leukemia: US Intergroup Trial E2997. *J Clin Oncol*. 2007;25(7):793-798.
11. Eichhorst BF, Busch R, Hopfinger G, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. *Blood*. 2006;107(3):885-891.
12. Catovsky D, Richards S, Matutes E, et al. Fludarabine Plus Cyclophosphamide Improves Response and Progression-Free Survival in Chronic Lymphocytic Leukemia. A Report from the LRF CLL4 Trial. *Lancet*. 2007;370:230-239.
13. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376(9747):1164-1174.

14. Tam CS, O'Brien S, Wierda W, et al. Long term results of the fludarabine, cyclophosphamide & rituximab regimen as initial therapy of chronic lymphocytic leukemia. *Blood*. 2008.
15. Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. *Blood*. 2007;109(2):405-411.
16. Keating M, O'Brien S, Albitar M, et al. Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab as Initial Therapy for Chronic Lymphocytic Leukemia. *J Clin Oncol*. 2005;23:4079-4088.
17. Ferrajoli A, O'Brien S M, Wierda W, al e. Treatment of patients with CLL 70 years old and older: a single center experience of 142 pateints. *Leuk Lymphoma*. 2005;46(S86).
18. Bosch F, Abrisqueta P, Villamor N, et al. Rituximab, Fludarabine, Cyclophosphamide, and Mitoxantrone a New, Highly Active Chemoimmunotherapy Regimen for Chronic Lymphocytic Leukemia. *J Clin Oncol*. 2009.
19. Wierda W, O'Brien SM, Faderl S, et al. CFAR, an active frontline regimen for high-risk patients with CLL, including those with Del 17p. *Blood*. 2008;112:2095(abstract).
20. Stevenson FK, Krysov S, Davies AJ, Steele AJ, Packham G. B-cell receptor signaling in chronic lymphocytic leukemia. *Blood*. 2011;118(16):4313-4320. Prepublished on 2011/08/06 as DOI 10.1182/blood-2011-06-338855.
21. Friedberg JW, Sharman J, Sweetenham J, et al. Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Blood*. 2010;115(13):2578-2585. Prepublished on 2009/12/08 as DOI 10.1182/blood-2009-08-236471.
22. Furman R, Byrd JC, Brown JR, et al. CAL-101, An Isoform-selective inhibitor of phosphatidylinositol 3-Kinase P110d, demonstrates clinical activity and pharmacodynamic effects in patients with relapsed or refractory chronic lymphocytic leukemia. *Blood*. 2010;116:Abstract #55.
23. Zent CS, LaPlant BR, Johnston PB, et al. The treatment of recurrent/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) with everolimus results in clinical responses and mobilization of CLL cells into the circulation. *Cancer*. 2010;116(9):2201-2207. Prepublished on 2010/02/19 as DOI 10.1002/cncr.25005.
24. Mohamed AJ, Yu L, Backesjo CM, et al. Bruton's tyrosine kinase (Btk): function, regulation, and transformation with special emphasis on the PH domain. *Immunological reviews*. 2009;228(1):58-73. Prepublished on 2009/03/18 as DOI 10.1111/j.1600-065X.2008.00741.x.
25. Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by Ibrutinib. *Blood*. 2011;117(23):6287-6296. Prepublished on 2011/03/23 as DOI 10.1182/blood-2011-01-328484.
26. Shanafelt TD, Bowen D, Venkat C, et al. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. *British Journal of Haematology*. 2007;39:255-264.

27. Else M, Smith AG, Cocks K, et al. Patients' experience of chronic lymphocytic leukaemia: baseline health-related quality of life results from the LRF CLL4 trial. *British Journal of Haematology*. 2008;143(5):690-697. Prepublished on 2008/11/20 as DOI 10.1111/j.1365-2141.2008.07407.x.
28. Eichhorst BF, Busch R, Obwandner T, Kuhn-Hallek I, Herschbach P, Hallek M. Health-Related Quality of Life in Younger Patients With Chronic Lymphocytic Leukemia Treated With Fludarabine Plus Cyclophosphamide or Fludarabine Alone for First-Line Therapy: A Study by the German CLL Study Group. *J Clin Oncol*. 2007.
29. Levy V, Porcher R, Delabarre F, Leporrier M, Cazin B, Chevret S. Evaluating treatment strategies in chronic lymphocytic leukemia: use of quality-adjusted survival analysis. *J Clin Epidemiol*. 2001;54(7):747-754.
30. Eichhorst BF, Busch R, Stilgenbauer S, et al. First line therapy with fludarabine compared to chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. *Blood*. 2009.
31. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol*. 1999;17(12):3835-3849.
32. Rawstron AC, Villamor N, Ritgen M, et al. International Standardized Approach for Flow Cytometric Residual Disease Monitoring in Chronic Lymphocytic Leukemia. *Blood*. 2006;In Press.

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Appendix I:**Blood Collection Kit Mayo Clinic CLL Laboratory**Specimen Checklist and Shipping Instructions**** PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS******Kit Contents:**

- Small Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- FedEx air bill with pre-printed return address
- Five 10mL Sodium Heparin (green) collection tubes
- Two 10mL Red Top collection tubes
- Absorbent tube holder
- Zip lock specimen bag

Packing and Shipping Instructions:

1. Collect the following specimens:

Peripheral blood – Draw:

- 50mL into five (5) Sodium Heparin tubes (**All Time Points**)
- 20mL in two (2) Red Top tubes (**Baseline, Twelve Month Response, and Fifteen Months After Randomization**)

2. All specimens are to be clearly labeled with the protocol number E1912, the patient's initials (last, first, middle), ECOG-ACRIN patient sequence number (if available) and date of collection.
3. Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
4. Place the filled specimen bag in the Styrofoam container.
5. Loosely pack with paper toweling.
6. Place the Styrofoam container and the Sample Tracking System shipping manifest form within the cardboard mailing sleeve.
7. Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx Air bill and adhere to the exterior lid of the box. Ship specimens via priority overnight delivery (next day delivery by 10am) the same day collected.
8. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

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The ECOG-ACRIN Sample Tracking System will automatically contact the CLL Laboratory. If your patient has not yet been registered and/or you did not use the ECOG-ACRIN Sample Tracking System please call Kim Henderson at (507) 284-3805 or e-mail Henderson.Kimberly@mayo.edu to notify the laboratory when samples are being shipped. Indicate the ECOG-ACRIN protocol number, the FedEx tracking number, and name and phone number of the contact person. The blood samples in prepared kits should be shipped to the following:

Kim Henderson
Mayo Clinic CLL Laboratory
613 Stabile
200 First Street Southwest
Rochester, MN 55905

Patient Information Form

It is required that samples submitted from patients participating in E1912 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (see Section 10.4). This form is used only in the event that the STS is inaccessible and then the shipments are to be logged in retroactively, indicating the actual dates of collection and shipment.

Specimen Date: / / _____

Institution/Affiliate: _____

Physician: _____

Patient Initials (last name, first name): _____

ECOG-ACRIN Protocol #: E1912 _____

ECOG-ACRIN Patient Sequence #: _____

Contact Person: _____

Institution: _____

Address: _____

	City	State	Zip
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Phone #: _____

FAX #: _____

Please indicate which samples are being shipped at this time and the Treatment Arm (2, 6 and 7):

1. Baseline
2. After Three (3) Cycles of Therapy
 - Arm A
 - Arm B
3. After Six (6) Cycles of Therapy (Prior to Cycle Seven) Arm A or (End of Cycle 6) Arm B
4. Twelve (12) Month Response Evaluation

5. 15 Months after Randomization
6. 18 Months after Randomization
7. 24 Months after Randomization
8. 36 Months after Randomization
9. Time of Disease Progression or Relapse

Any questions concerning these samples or to obtain blood collection kits for the E1912 study, please contact:

Kim Henderson
Mayo Clinic CLL Laboratory
(507) 284-3805
Henderson.Kimberly@mayo.edu

Affiliates who anticipate participating in this study should please call in advance for kits.

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We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at <http://www.ecog.org>. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME]

[DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of **[INSTITUTION]** and the ECOG-ACRIN, we thank you again.

Sincerely,

[PHYSICIAN NAME]

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).**Appendix III:****Ibrutinib Patient Medication Calendar**

Ibrutinib should be taken with 8 ounces of water.

Pill Calendar Directions

1. Take your scheduled dose of each capsule.
2. Doses are to be taken at about the same time each day. If an ibrutinib dose is missed, it should be made up as soon as possible on the same day with a return to the normal schedule the following day. If you forget to take your medication for a day (or several days), please just restart your medicine at the usual dose and do not attempt to 'make-up' any missed doses.
3. Please bring the empty bottle or any leftover capsules and your medication calendar to your next clinic visit.

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Ibrutinib Patient Medication Calendar

This is a calendar on which you are to record the time and number of capsules you take each day. You should take your scheduled dose of each capsule. **Note the times and the number of capsules that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused capsules and your completed medications calendar to your doctor’s visits.

DAY	Date			Time capsules taken		Number of capsules taken		Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year	AM	PM	AM	PM	
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
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E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).**Appendix IV:****CRADA/CTA**

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (<http://ctep.cancer.gov/industry>) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: <http://ctep.cancer.gov>.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):
 - a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
 - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
 - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

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Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).**Appendix V:****ECOG Performance Status**

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 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.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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Appendix VI:

Grading Scale for Hematologic Toxicity in CLL Studies

The following toxicity grading guidelines apply for patients with baseline hematologic toxicity.

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Decrease from Pretreatment value (%)	Grade ²	
	Platelets ^{3,5}	Hemoglobin ^{4,5}
No change - 10%	0	0
11-24%	1	1
25-49%	2	2
50-74%	3	3
≥ 75%	4	4

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1. Grades: 1–mild; 2–moderate; 3–severe; 4–life–threatening. Grade 5 (fatal) toxicity can potentially occur at any level of decrease from pretreatment values and will be recorded as such.
2. If, at any level of decrease the platelet count is < 20,000/μL, this will be considered grade 4, unless the initial platelet count was ≤ 20,000 μL in which case the patient is inevaluable for toxicity referable to platelet counts.
3. Baseline and subsequent hemoglobin determinations must be immediately prior to any given transfusions.
4. If, at any level of decrease from the baseline value the platelet and/or hemoglobin counts are within normal limits, this will be considered a grade 0.

Hallek BD, et al.: Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer-Institute- Working Group 1996 guidelines: Blood 111:54465456, 2008.

Hematologic Toxicity Grading Worksheet

<u>Decrease in platelets or hemoglobin from pretreatment value</u>	<u>Grade</u>	<u>Platelets</u>	<u>Hemoglobin</u>
Baseline			
No Change – 10%	0		
11 – 24%	1		
25 – 49%	2		
50 – 74%	3		
≥ 75%	4		

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Appendix VII:

Cumulative Illness Rating Scale

Rating Strategy of Comorbidity		
0	No problem	Organ system not compromised.
1	Mild	Illness/impairment with or without requirement of therapy, excellent prognosis, patient with normal activity.
2	Moderate	Illness/impairment requiring therapy, good prognosis, comprised activity of patient.
3	Severe	Illness/impairment with urgent requirement of therapy, prognosis unclear, marked restriction in activity.
4	Extremely severe	Life threatening illness/impairment, emergency case of therapy, adverse prognosis.

Please take into account that CLL induced illness or organ damage are not included in this rating scale! The goal of this rating scale is to assess comorbidity other than CLL in the patient. If there are two or more illnesses/impairments of one organ system, the illness/impairment with the highest severity should be evaluated!

Organ System	A) If illness/impairment present, please specify	B) Score
1. Heart		<input type="checkbox"/>
2. Blood pressure		<input type="checkbox"/>
3. Vascular		<input type="checkbox"/>
4. Respiratory		<input type="checkbox"/>
5. Ear/nose/throat		<input type="checkbox"/>
6. Upper gastrointestinal		<input type="checkbox"/>
7. Lower gastrointestinal		<input type="checkbox"/>
8. Liver		<input type="checkbox"/>
9. Renal		<input type="checkbox"/>
10. Genitourinary		<input type="checkbox"/>
11. Musculoskeletal		<input type="checkbox"/>
12. Endocrine/metabolic		<input type="checkbox"/>
13. Neurological		<input type="checkbox"/>
14. Psychiatric		<input type="checkbox"/>
15. Score:	Total	<input type="checkbox"/> <input type="checkbox"/>

Extermann et al JCO 16: 1582–1587,

E1912: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).

Appendix VIII:

CYP3A Inhibitors and Inducers

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The medications or substances that are listed in the table below are **strong or moderate inhibitors** of CYP3A4.

Strong and moderate inhibitors of CYP3A4/5 should also be avoided while taking ibrutinib.

If patients require treatment with strong or moderate inhibitors of CYP3A4 that are used after registration see Section [8.1.11](#) for additional information on monitoring and Ibrutinib dosing.

Please also consult a frequently updated reference for a comprehensive list of inhibitors, inducers, and substrates.

Inhibitors of CYP3A	Inducers of CYP3A
<u>Strong inhibitors:</u>	Carbamazepine
INDINAVIR	Efavirenz
NELFINAVIR	Nevirapine
RITONAVIR	Barbiturates
CLARITHROMYCIN	Glucocorticoids
ITRACONAZOLE	Modafinil
KETOCONAZOLE	Oxcarbazepine
NEFAZODONE	Phenobarbital
SAQUINAVIR	Phenytoin
SUBOXONE	Pioglitazone
TELITHROMYCIN	Rifabutin
<u>Moderate inhibitors:</u>	Rifampin
Aprepitant	St. John's Wort
Erythromycin	Troglitazone
diltiazem	
Fluconazole	
grapefruit juice	
Seville orange juice	
Verapamil	
<u>Weak inhibitors:</u>	
Cimetidine	
<u>All other inhibitors:</u>	
Amiodarone	
NOT azithromycin	
Chloramphenicol	
Boceprevir	
Ciprofloxacin	
Delavirdine	
diethyl-dithiocarbamate	
Fluvoxamine	
Gestodene	

Imatinib	
Mibefradil	
Mifepristone	
Norfloxacin	
Norfluoxetine	
star fruit	
Telaprevir	
Troleandomycin	
Voriconazole	

Receiving any medications or substances that are **inducers** of CYP3A4.

Use of the following above are prohibited ≤ 7 days prior to registration.

INHIBITORS OF CYP3A4/5:

1. use of strong CYP3A4/5 inhibitors (such as indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, ketoconazole, itraconazole, and nefazodone) should be avoided while on Ibrutinib.
2. Moderate CYP3A4/5 inhibitors (aprepitant, erythromycin, fluconazole, verapamil, and diltiazem) should be used with caution while on Ibrutinib.
3. Grapefruit juices and Seville oranges may also increase Ibrutinib plasma concentrations and should be avoided for the duration of Ibrutinib treatment.

For Patient Use While Taking Ibrutinib (PCI-32765)

INFORMATION ON POSSIBLE DRUG INTERACTIONS

You are enrolled on a clinical trial using the experimental agent _____ . This clinical trial is sponsored by the NCI. _____ interacts with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.
- Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial.
- You should avoid supplements such as fish oils and vitamin E; check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

_____ interacts with a specific liver enzyme called **CYP_____**, and must be used very carefully with other medicines that interact with this enzyme.

- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP_____**."
- Before prescribing new medicines, your regular prescribers should go to <http://medicine.iupui.edu/clinpharm/ddis/table.aspx> for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____

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Rev. 1/16**Appendix IX:****Instructions for Reporting Pregnancies on a Clinical Trial****What needs to be reported?**

Although not an adverse event in and of itself, pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease status) occurring in a female patient or a female partner of a male patient while the subject is on Ibrutinib, or within 90 days of the subjects last dose of Ibrutinib, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP's Adverse Event Reporting System (CTEP-AERS)

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERS report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERS report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Center. Please contact the ECOG-ACRIN Operations Center to ask for a conference call to be set up with the appropriate individuals.

- It is recommended the female be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERS report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* CTEP-AERS report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com for it will need to be discussed on a case by case basis.

Rev. Add8 Reporting a Pregnancy Loss

A pregnancy loss is defined in CTCAE as “*A death in utero.*”

It must be reported via CTEP-AERS as Grade 4 “*Pregnancy loss*” under the System Organ Class (SOC) “*Pregnancy, puerperium and perinatal conditions*”.

A fetal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient’s death.

Rev. Add8 Reporting a Neonatal Death

A neonatal death is defined in CTCAE as “*A death occurring during the first 28 days after birth*” that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERS AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to Ibrutinib must also be reported via CTEP-AERS.

It must be reported via CTEP-AERS as Grade 4 “*Death Neonatal*” under the System Organ Class (SOC) “*General disorder and administration site conditions*”.

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient’s death.

Additional Required Forms:

When submitting CTEP-AERS reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP 'Pregnancy Information Form'** must be completed and faxed along with any additional medical information to CTEP (301-230-0159). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

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Appendix X:

Timed Up and Go (TUG) Test^{1,2}

1. Equipment: arm chair, tape measure, tape, stop watch.
2. Begin the test with the subject sitting correctly in a chair with arms, the subject's back should resting on the back of the chair. The chair should be stable and positioned such that it will not move when the subject moves from sitting to standing.
3. Place a piece of tape or other marker on the floor 3 meters away from the chair so that it is easily seen by the subject.
4. Instructions: "On the word GO you will stand up, walk to the line on the floor, turn around and walk back to the chair and sit down. Walk at your regular pace.
5. Start timing on the word "GO" and stop timing when the subject is seated again correctly in the chair with their back resting on the back of the chair.
6. The subject wears their regular footwear, may use any gait aid that they normally use during ambulation, but may not be assisted by another person. There is no time limit. They may stop and rest (but not sit down) if they need to.
7. Normal healthy elderly usually complete the task in ten seconds or less. Very frail or weak elderly with poor mobility may take 2 minutes or more.
8. The subject should be given 1 untimed practice effort followed by a single timed effort before testing.
9. Results correlate with gait speed, balance, functional level, the ability to go out, and can follow change over time.
10. Interpretation
 - ≤ 10 seconds = normal
 - ≤ 20 seconds = good mobility, can go out alone, mobile without a gait aid.
 - < 30 seconds = problems, cannot go outside alone, requires a gait aid.

A score of more than or equal to fourteen seconds has been shown to indicate high risk of falls.

1. Podsiadlo D, Richardson S. *The Time "Up & Go": A Test of Basic Functional Mobility for Frail Elderly Persons*. Journal of the American Geriatrics Society 1991; 39(2): 142-148
2. Shumway - Cook A, Brauer S, Woollacott M. *Predicting the Probability for Falls in Community-Dwelling Older Adults Using the Timed Up & Go Test*. Physical Therapy 2000 Vol 80(9): 896-903.
Saskatoon Falls Prevention Consortium, Falls Screening and Referral Algorithm, TUG, Saskatoon Falls Prevention consortium, June, 2005

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Appendix XI:

RAI Staging

Both CLL and SLL patients should be staged according to the Rai system.

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NOTE: the presence or absence of lymphadenopathy, splenomegaly, and hepatomegaly in assignment of Rai stage is based on physical exam only (not CT scan results).

CLL Patients: CLL patients should be classified as stage 0-IV according to the most unfavorable characteristic present according to below:

Stage 0	Lymphocytosis only without lymphadenopathy, hepatosplenomegaly, anemia (hemoglobin < 11 g/dL) or thrombocytopenia (platelets < 100 × 10 ⁹ /L)
Stage I	Lymphadenopathy without hepatosplenomegaly, anemia, or thrombocytopenia.
Stage II	Splenomegaly +/- lymphadenopathy
Stage III	Anemia (hemoglobin < 11 g/dL) with or without lymphadenopathy, hepatomegaly, or splenomegaly)
Stage IV	Thrombocytopenia (platelets < 100 × 10 ⁹ /L) with or without lymphadenopathy, hepatomegaly, splenomegaly, or anemia.

SLL Patients: Since, by definition, patients with SLL have lymphadenopathy and an absolute lymphocyte count < 5, they cannot be classified as stage 0. Accordingly, patients with SLL should be classified as stage I-IV according to the most unfavorable characteristic present according to below:

Stage I	Lymphadenopathy without hepatosplenomegaly, anemia, or thrombocytopenia.
Stage II	Splenomegaly +/- lymphadenopathy
Stage III	Anemia (hemoglobin < 11 g/dL) with or without lymphadenopathy, hepatomegaly, or splenomegaly)
Stage IV	Thrombocytopenia (platelets < 100 × 10 ⁹ /L) with or without lymphadenopathy, hepatomegaly, splenomegaly, or anemia.

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Appendix XII:**CHILD-PUGH SCORE**

Measure	1 point	2 points	3 points
Total bilirubin, $\mu\text{mol/L}$ (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.

Pugh RN, Murray-Lyon IM, Dawson L, et al . "Transection of the oesophagus for bleeding oesophageal varices". The British journal of surgery, 1973;60: 646-9.

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Addendum #1 includes the following changes in the Protocol:

1.	Cover page	
2.	Global change throughout protocol	Revised reference of “ECOG” to “ECOG-ACRIN,” “ECOG Coordinating Center” to “ECOG-ACRIN Coordinating Office” and “Eastern Cooperative Oncology Group” to “ECOG-ACRIN Cancer Research Group.”
3.	Section 5.1.3.7, page 28, last paragraph	Updated language throughout to reflect all salvage therapy treatment and removed last sentence of paragraph.
4.	Section 5.2.11, page 39	Replaced “ECOG Second Primary Form” with “Second Primary Form” in 1st, 2nd and 3rd NOTE for administration simplification.
5.	Section 7.1, pages 57-58, table	Inserted X’s in the “Follow Up” row to reflect required tests and procedures and inserted footnote reference (15) to “Follow Up” header. Removed “glucose” from the first column, row 17. Inserted footnote reference (14) to “During Treatment” header and under “Test/Procedures” column in rows 5, 6, 9, 10, 11, 15, 18, 22, 25, 26, 30, 32. Inserted.
6.	Section 7.1, page 59	Inserted footnote 14 to address patients coming off treatment for any reason other than progression.
7.	Section 7.1, page 59	Inserted footnote 15 to provide follow-up schedule.
8.	Appendix X, page 106, item 8	Replaced “a practice trial that is not timed” with “1 untimed practice effort followed by a single timed effort.”

Addendum #2 includes the following changes in the Protocol:

1.	Cover Page	Updated Version Date. Removed “ECOG-ACRIN Cancer Research Group” title, as it is noted in logo. Updated CALGB Co-Chair. Removed NCIC Co-Chair line, as it was blank. Updated participating organizations’ names to comply with NCTN guidelines.
2.	Global Changes	Changed references to “ECOG-ACRIN Coordinating Office” to “ECOG-ACRIN Operations Office – Boston.” General spelling and administrative edits made throughout.
3.	"CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION" Section	Revised language throughout to reflect updated CTSU requirements.
4.	Schema	Revised stratification factor from "11q23" to read "11q22.3(ATM)" as it was previously incorrect.
5.	Section 3.1.11	Removed last NOTE to reflect the closure of E3903.
6.	Section 3.1.9	Revised the language in the 1st requirement to clarify requirement and included the Cockcroft-Gault equation.

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7.	Section 4	Revised language throughout to reflect updated CTSU requirements and the ability for patients to be enrolled via OPEN.
8.	Section 4.5.4	Revised "11q23" to read "11q22.3(ATM)" as it was previously incorrect.
9.	Section 4.6	Replaced the last NOTE of Section 4.6.1 with revised language to reflect the closure of E3903. Removed Section 4.6.3 in its entirety to reflect the closure of E3903. The subsequent sections have been renumbered accordingly.
10.	Section 4.6.3	Removed the last sentence of the 1st note.
11.	Section 5.1	Inserted the last NOTE in its entirety to detail dose rounding guidelines.
12.	Section 5.1.1.2	Replaced "Cycles 1-6" with "Cycles 2-7" and "Cycle 1" with "Cycle 2" as it was previously incorrect.
13.	Section 5.1.1.3	Revised the 1st sentence from "Cycles 1-3" to "Cycles 1 and 2" as it was previously incorrect.
14.	Section 5.1.2	Replaced language in the 1st sentence of the 2nd paragraph for clarification.
15.	Section 5.1.3.6	Reformatted first sentence, as it was previously at the end of 5.1.3.5. Revised the end of the last sentence of the 3rd paragraph for clarification.
16.	Section 5.2	Revised entire section to reflect the change from AdEERS to CTEP-AERS system.
17.	Section 5.3.1	Replaced "AdEERS" with "CTEP-AERS."
18.	Section 5.4.9	Inserted Section 5.4.9 in its entirety to clarify guidelines for infusion reactions to rituximab.
19.	Section 6.1.3.5	Removed "As detailed in Section 6.1.3.5" from the 2nd paragraph as it was inserted unnecessarily.
20.	Section 7.1	Removed NOTE prior to table.
21.	Section 7.1	Table: Inserted "+/- 4 days" to the 3rd column, 3rd row and 4th column, 3rd row. Inserted "+/- 7 days" to the 5th column, 3rd row. Revised the title of the 1st column, 16th row for clarification and added footnote reference "16," Revised the title of the 1st column, 26th row to read "Hepatitis C Anti-body testing" as it was previously incorrect.

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22.	Section 7.1	Footnote 8: Revised language to clarify baseline bone marrow biopsy requirements. Footnote 10: Revised language to clarify that QOL is still collected after progression. Footnote 16: Inserted in its entirety.
23.	Section 7.2	Revised text, table and footnotes to reflect additional collection and submission requirements and the closure of E3903. Table: Inserted "15" into the title line of the 6th row, as an additional blood sample is requested at this time point and last two rows.
24.	Section 7.2	Removed footnote 4 and inserted footnotes 5 and 6 in their entirety.
25.	Section 9	Revised "11q23" to read "11q22.3(ATM)" three times throughout the section, as it was previously incorrect.
26.	Section 9.1	Revised the 6th bullet point for clarification.
27.	Section 9.7	Removed the 8th paragraph.
28.	Section 10	Revised the entire section to reflect additional collection and submission requirements and the closure of E3903.
29.	Section 10.1	Revised the submission and shipping procedures to reflect new guidelines.
30.	Section 10.2	Revised the submission and shipping procedures to reflect new guidelines. Inserted "15" into the title line of the 6th row in the first table, as an additional blood sample is requested at this time point.
31.	Section 10.2.2	Revised section to reflect updated packing instructions.
32.	Section 10.4	Removed the 1st sentence of the 3rd paragraph and included "to Mayo Clinic only" to the 1st paragraph of the "Study Specific Notes."
33.	Section 10.5	Replaced "the bone marrow and peripheral blood samples" with "specimens."
34.	Appendix I	Inserted updated shipping requirements and packing instructions. Revised the Patient Information Form to reflect new guidelines.
35.	Appendix IX	Revised entire section to reflect the change from AdEERS to CTEP-AERS system.

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Addendum #3 includes the following changes in the Protocol:

1.	Cover Page	Updated Version Date. Deleted NOTE regarding CTSU and non-ECOG-ACRIN sites.
2.	Global Changes	General spelling and administrative edits made throughout.
3.	Section 3.1.18	Added eligibility language regarding Hepatitis B patients who are HBcAb positive and Hepatitis B DNA negative.
4.	Section 5.1.1	Replaced “following” with “beginning” for procedural clarification. Added third NOTE regarding antibiotic prophylaxis.
5.	Section 5.1.1.1	Inserted 4th bullet point under Cycles 2-7 to provide clarification for distribution of ibrutinib.
6.	Section 5.1.1.2	Inserted language to the 2nd bullet point for the use of alternative anti-histamines to reduce infusion reactions.
7.	Section 5.1.1.5	Inserted language regarding administration modifications for rituximab on day 1 of cycle 2 and day 1 of cycles 3-7. In day 1 of cycles 3-7 paragraph the infusion rate was changed to 100 mg/hr.
8.	Section 5.1.3	Added NOTE regarding antibiotic prophylaxis.
9	Section 5.1.3.3	Removed “BUN” from 4th bullet down since this test is not required.
10.	Section 5.1.3.4	Inserted language regarding administration modifications for day 1 of cycle 1, day 2 of cycle 1, and day 1 of cycles 2-6. In day 1 of cycles 2-6 paragraph, the infusion rate was changed to 100 mg/hr.
11.	Section 5.2.2	Added language clarifying the reporting requirements for the SPEER and expedited reporting.
12.	Section 5.2.3	Per CTEP recommendations, added “CTEP/NCI” and Arm B to reporting requirements to the second bullet. Deleted FDA reporting requirements.
13.	Section 5.2.5.2	Per CTEP recommendations, added “considered important medical event” to second bullet point. Added “only if meets serious criteria” to third bullet point.
14.	Section 5.2.7	Added language clarifying the reporting requirements for the SPEER and expedited reporting. Inserted language regarding hemorrhagic events.
15.	Section 5.2.8	7th box down in flow chart, changed language to “Report event via CTEP-AERS”.
16.	Section 5.3.1	Edited NOTE regarding the SPEER and expedited reporting.
17.	Section 5.4.3	In second paragraph, inserted time constraint of 56 days regarding recovery of blood counts and continuation of therapy for Arm B.
18.	Section 5.4.4	In second paragraph, inserted time constraint of 56 days regarding recovery of blood counts and continuation of therapy for Arm B.
19.	Section 5.4.5	In second paragraph, inserted time constraint of 56 days regarding recovery of blood counts and continuation of therapy for Arm B.

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20.	Section 5.4.7	Inserted 7th bullet point regarding dose reduction for non-hematologic toxicity.
21.	Section 6.1	Added 2nd paragraph to provide procedural clarification for the physical exam.
22.	Section 6.1.1.1	Inserted further guidance for determining Complete Remission.
23.	Section 6.1.1.5	Inserted sentence requiring only a single BM exam to document CR.
24.	Section 7.1	1st column, row 15, added footnote 5 and 14 references; 1st column, row 17, added “potassium, LDH”; 1st column, row 19, added “on peripheral blood or bone marrow”; 1st column, 28th row, changed footnote reference from 14 to 12; 3rd column, 3rd row added footnote 19 reference; 3rd column, rows 5, 9, 10, 11 added footnote 18 reference; 7th column, 2nd row, deleted “observation and/or” and added "Continuation17". Footnote 2 edited to read “must measure” and “must record” along with measurement clarifications. Footnote 5 edited to indicate when tests should be completed. Footnote 7, added 2nd sentence. Footnote 9 edited to indicate when tests should be completed and added linking to 3.1.18. Footnote 11 edited to change “antigen” to “anti-body” and added timeframe for tests. Footnote 12, removed “at the discretion of the study chair,” added CT scan time parameters, and added clarified CT scan requirements. Footnote 14, added “within 2 weeks” for response evaluation of patients with progressive disease. Footnote 15, edited timing of long term follow-up. Footnotes 17, 18, and 19 inserted in their entirety.
25.	Section 7.2	2nd column, 1st row, deleted footnote reference. 2nd column, rows 2-6 added footnote 1 reference. 6th column, 7th row: inserted “X” and reference to footnote 7. Inserted submission guidelines to footnote 5. Inserted footnote 7 in its entirety.
26.	Section 9.7	Inserted 8th paragraph regarding immune system evaluation and pneumococcal vaccination.
27.	Section 10.1.1	Biological Materials table: Inserted footnote 4 reference to 1st column, row 3; inserted “submitted” to footnote 1; inserted footnote 4 in its entirety.
28.	Section 10.1.3	Changed submission of marrow sections/slides from “within one month of collection” to “within one month of randomization.”
29.	Section 10.2.1	Inserted “X” to 6th column, 3rd row. 6th column, 4th row: inserted reference to footnote 2. Inserted footnote 2 in its entirety.
30.	Section 10.3.9	Section regarding Pevnar vaccine inserted in its entirety.
31.	Appendix I	Amended timeline for collection of peripheral blood specimens.
32.	Appendix III	Edited direction 2 to clarify procedures for missed doses of ibrutinib.
33.	Appendix IV	Deleted physical address and fax for manuscript reporting.

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34.	Appendix VI	Added 1st sentence regarding purpose of guidelines. Deleted first note.
35.	Appendix VIII	In 6th box changed “weak inhibitors” to “weak inducers”.
36.	Appendix XI	RAI staging inserted in its entirety

Addendum #4 includes the following changes in the Protocol:

	Section	Change
1.	Cover Page	Updated Version Date.
2.	Section 1.3	Ibrutinib safety update inserted in its entirety.
3.	Section 3.1.2	Inserted “ BTK inhibitor therapy”.
4.	Section 3.1.9	Updated eligibility measurements for SGOT(AST)/SGPT(ALT). Inserted requirement for PT/INR.
5.	Section 3.1.15	Updated language regarding timelines for major/minor surgeries
6.	Section 3.1.18	Updated list of exclusions for patient conditions.
7.	Section 3.1.19	Updated language for cytochrom P450 (CYP) 3A inhibitor.
8.	Section 3.1.22	Updated language regarding females of childbearing potential.
9.	Section 3.1.24	Inserted requirement in its entirety.
10.	Section 3.1.25	Inserted requirement in its entirety.
11.	Section 3.1.26	Inserted requirement in its entirety.
12.	Section 3.1.27	Inserted requirement in its entirety.
13.	Section 3.1.28	Inserted requirement in its entirety.
14.	Section 5.1.1	Inserted 2nd note regarding dose modifications to ibrutinib if patients require treatment with a CYP3A inhibitor/inducer.
15.	Section 5.2.7	Updated reporting requirements for pregnancy. Deleted “Intracranial hemorrhage” from other adverse events list.
16.	Section 5.3	Inserted updated CAEPR for study drug ibrutinib.

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17.	Section 5.4.3	Arm A: changed M500/mL" to "500/μL". Deleted first sentence regarding holding ibrutinib for 28 days. Deleted sentence requiring dose reductions be maintained through all future cycles. Inserted paragraph regarding re-escalation of ibrutinib after a dose reduction due to toxicity. Arm B: added "Arm B" to NOTE.
18.	Section 5.4.4	Arm B: added "Arm B" to NOTE.
19.	Section 5.4.5	Arm A: Deleted first sentence regarding holding ibrutinib for 28 days. Deleted sentence requiring dose reductions be maintained through all future cycles. Inserted paragraph regarding re-escalation of ibrutinib after a dose reduction due to toxicity. Arm B: added "Arm e" to NOTE.
20.	Section 5.4.6	Section regarding dose modifications for Atrial Fibrillation inserted in its entirety. Subsequent sections have been renumbered as a result.
21.	Section 5.4.8	4th bullet: deleted sentence regarding toxicity lasting longer than 28 days. 5th note: deleted in its entirety and a new 5th note was inserted to replace previous language. Arm A: Inserted sentence below table.
22.	Section 5.4.11	Inserted section in its entirety.
23.	Section 5.5.7	Inserted section in its entirety.
24.	Section 5.5.8	Inserted section in its entirety.
25.	Section 5.5.9	Inserted section in its entirety.
26.	Section 5.5.10	Inserted section in its entirety.
27.	Section 5.5.11	Inserted section in its entirety.
28.	Section 5.5.12	Inserted section in its entirety.
29.	Section 5.5.13	Inserted section in its entirety.
30.	Section 7.1	Inserted "PT/INR, PTT (aPTT)" test and subsequent collection timepoints.
31.	Section 8.1.12	Updated language regarding potential interactions.
32.	Section 8.1.13	Inserted Overdose section in its entirety.
33.	Appendix VIII	Updated list of CYP3A Inhibitors/Inducers
34.	Appendix IX	Updated reporting requirements for pregnancies.
35.	Appendix XII	Inserted appendix for Child-Pugh Score in its entirety.

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Addendum #5 includes the following changes in the Protocol:

	Section	Change
1.	Cover Page	Updated version date. Added CCTG to Study Participants.
2.	Global Changes	General formatting and edits. Updated “Leukemia Translational Studies Laboratory” to “Leukemia Translational Research Laboratory” and relevant contact information throughout protocol.
3.	CTSU Table	Deleted paragraph box second from the bottom.
4.	Section 4	Updated CTSU regulatory information.
5.	Section 4.6.4	Inserted last two paragraphs regarding the remote monitoring activities with Alpha Oncology.
6.	Section 5.4.8	Removed language requiring study medication to be permanently discontinued if interrupted for more than 60 days. Changed to make 42 day interruption the maximum.
7.	Section 5.4.9	Updated language regarding anticoagulation therapy and ibrutinib treatment.
8.	Section 5.4.11	Inserted language regarding ibrutinib and hepatic impairment.
9.	Section 6.1.3.1	Inserted language to clarify Progression Disease requirements.
10.	Section 6.1.3.2	Inserted language to clarify Progression Disease requirements.
11.	Section 7.1	2 nd Row, 6 th Column: increased window to “+/- 4 weeks”; 5 th Row, 3 rd column: inserted reference to 18 th footnote; Footnote 6: changed “7 days prior to registration” to “14 days prior to registration” to be consistent with eligibility criteria; Footnote 14: Added “or completion of treatment per protocol (Arm B)” for clarification purposes.
12.	Section 7.2	3 rd row, 1 st column: inserted “biopsy”. Footnote 5: inserted “biopsy” and amended “can be submitted” to “are to be submitted”.
13.	Section 8.1.12	Updated language regarding use ibrutinib and interactions with CYP3A4 and CYP3A inhibitors. Updated language regarding interactions with supplements such as vitamin E preparations and fish oils.
14.	Section 9	Updated statistical interim analysis based on faster than expected rate of accrual.
15.	Section 10.1.1	Inserted “biopsy” throughout section. Added 3 rd NOTE regarding bone marrow biopsy sections/slides.

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16.	<u>Section 10.1.2</u>	Distinguished guidelines for Bone Marrow Smears and Bone Marrow Biopsy Sections/Slides. Inserted second NOTE regarding bone marrow biopsy sections/slides.
17.	<u>Section 10.1.3</u>	Inserted “biopsy” and changed “registration” to “randomization” to the pre- trial diagnostic bone marrow paragraph. Added label instructions to 2 nd to last paragraph.
18.	<u>Section 10.1.3.1</u>	Inserted “biopsy”.
19.	Appendix VI	Changed language to indicate appendix should be used for patients with baseline hematologic toxicity.
20.	<u>Appendix XI</u>	Inserted note to indicate RAI staging is based on physical exam

Addendum #6 includes the following changes in the Protocol:

	Section	Change
1.	<u>Cover Page</u>	Updated Version Date.
2.	<u>Section 5.2.7</u>	Inserted language for Risk Mitigation Plan.
3.	<u>Section 5.3</u>	Updated the Ibrutinib CAEPR to Version 2.4, October 12, 2016.

Addendum #7 includes the following changes in the Protocol:

	Section	Change
1.	<u>Cover Page</u>	Updated Version Date.
2.	<u>Section 5.3</u>	Updated the Ibrutinib CAEPR to Version 2.5, May 25, 2017.

Addendum #8 includes the following changes in the Protocol:

	Section	Change
1.	<u>Cover Page</u>	Updated Version Date.
2.	<u>Section 5.3</u>	Updated the Ibrutinib CAEPR to Version 2.6, January 29, 2018.

Original Statistical Plan

Please refer to original protocol section 9.

Final Statistical Plan

Please refer to final protocol section 9.

Summary of Changes

Addendum #2 includes the following changes in Section 9, Statistical Considerations.

25.	Section 9	Revised "11q23" to read "11q22.3(ATM)" three times throughout the section, as it was previously incorrect.
26.	Section 9.1	Revised the 6th bullet point for clarification.
27.	Section 9.7	Removed the 8th paragraph.

Addendum #3 includes the following changes in Section 9, Statistical Considerations.

26.	Section 9.7	Inserted 8th paragraph regarding immune system evaluation and pneumococcal vaccination.
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Addendum #5 includes the following changes in Section 9, Statistical Considerations.

14.	Section 9	Updated statistical interim analysis based on faster than expected rate of accrual.
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