Update #08

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO A041202

A RANDOMIZED PHASE III STUDY OF BENDAMUSTINE PLUS RITUXIMAB VERSUS IBRUTINIB PLUS RITUXIMAB VERSUS IBRUTINIB ALONE IN UNTREATED OLDER PATIENTS (≥ 65 YEARS OF AGE) WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Clinicaltrials.gov identifier: NCT01886872
NCI-supplied agent: Ibrutinib (NSC #748645, IND #117241);
Commercial agent(s): Rituximab and Bendamustine

[X] **Update:**	[ ] **Status Change:**
[ ] Eligibility changes	[ ] Activation
[ ] Therapy / Dose Modifications / Study Calendar changes	[ ] Closure
[X] Informed Consent changes	[ ] Suspension / temporary closure
[ ] Scientific / Statistical Considerations changes	[ ] Reactivation
[X] Data Submission / Forms changes	
[X] Editorial / Administrative changes	
[ ] Other :	

Expedited review is allowed. IRB approval (or disapproval) is required within 90 days.
Please follow your IRB of record guidelines.

UPDATES TO THE PROTOCOL:

Cover Page (Page 1)

- Cancer in the Elderly has been renamed as Cancer in the Older Adult.
- Dr. Jennifer Le-Rademacher has replaced Dr. Arti Hurria as Cancer in the Older Adult Co-Chair (formerly Cancer in the Elderly). All contact information has been updated.
- All contact information for Amy S. Stark (formerly Amy S Ruppert) has been updated.
- Diane Feldman has replaced Samantha Sublett as the Protocol Coordinator. All contact information has been updated.

- Brandon Bright has replaced Luke Wilson as the Data Manager. All contact information has been updated.
- NCIC-CTG/NCIC Clinical Trials Group has been renamed CCTG/Canadian Cancer Trials Group under Participating Organizations.

Study Resources (Page 2)

- Page 2 has been titled Study Resources to reflect current CTSU boilerplate language.
- Participating Groups has been renamed to Study Champions to reflect current CTSU boilerplate language.
- NCIC has been renamed CCTG.
- Carolyn Owen has replaced Stephen Couban as the CCTG (formerly NCIC) Study Champion. All contact information has been updated.
- The contact information for the participating groups' operations offices for ECOG-ACRIN, CCTG (formerly NCIC), and SWOG has been removed as this information is out of date and all protocol-related questions should be directed to the lead protocol organization (Alliance).

CTSU Contact Information (Page 3)

The CTSU Contact Information table has been updated with current CTSU boilerplate language.

Section 5.3 (Registration Procedures)

- Section 5.3.1 (CTEP Investigator Registration Procedures) and Section 5.3.2 (CTEP Associate Registration Procedures / CTEP-IAM Account) have been removed and replaced with a new Section 5.3.1 entitled "CTEP Registration Procedures" which includes updated CTSU boilerplate language. Subsequent sections have been renumbered accordingly.
- All text in Section 5.3.2 (CTSU Registration Procedures) (formerly Section 5.3.3) has been completely revised to include updated CTSU boilerplate language.

Section 7.0 (Required Data)

- In the Day 1 of Every Third Cycle During Treatment, Arm 1 Observation & Clinical Follow-up column, the following laboratory studies have changed from "X" to "A."
    - Serum creatinine, CrCl (est.), BUN, Serum electrolytes, AST, ALT, PT INR, alk. phos., bilirubin, LDH, and albumin
- Footnote A language has been updated from "Ongoing solicited adverse event forms are only necessary..." to "Ongoing solicited adverse even forms and indicated laboratory studies are only necessary…" in order to reflect the changes made in the required data table.
- Footnote ** language has been updated to reflect that patients continuing to receive ibrutinib with "Arms 2 and 3" replacing "Arms 1 and 2."

Section 11.2 (Ibrutinib [PCI-32765, NSC # 748645, IND #117241])

Subheading "*Agent Ordering*" had been renamed as "*Agent Ordering and Agent Accountability*." All text in subheading "*Agent Ordering and Agent Accountability*" (formerly *Agent Ordering*) has been completely revised to include updated CTSU boilerplate language.

Appendix III (Registration Fatigue/Uniscale Assessments)

In the third paragraph, NCIC has been revised with CCTG to reflect NCIC has been renamed.

UPDATES TO THE MODEL CONSENT:

What will happen if I take part in this research study?

In the second paragraph under "When you are finished taking the study drugs, and/or when you are continuing on ibrutinib…" the timing of the Cycle 9 Day 1 blood tests and bone marrow biopsy have been corrected from "Nine months after you start treatment" to "Eight months…" for consistency.

What side effects or risks can I expect from being in the study?

Under "Risks and side effects related to ibrutinib include those which are," incorrectly presented the patient ratio for "Occasional, some may be serious" in the condensed risk profile table. The correct patient ratio for "Occasional, some may be serious" is "from 4 to 20" has replaced "more than 20 and up to 100."

A replacement protocol document and model consent have been issued.
This study remains closed to new patient accrual.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A041202

A RANDOMIZED PHASE III STUDY OF BENDAMUSTINE PLUS RITUXIMAB VERSUS IBRUTINIB PLUS RITUXIMAB VERSUS IBRUTINIB ALONE IN UNTREATED OLDER PATIENTS (≥ 65 YEARS OF AGE) WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Clinicaltrials.gov identifier: NCT01886872
NCI-supplied agent: Ibrutinib (NSC #748645, IND #117241);
Commercial agent(s): Rituximab and Bendamustine

Required Embedded Correlative Science Companion Study: Alliance A041202-LC1
Optional Companion Studies: CALGB 9665(temporarily suspended on February 28, 2014), Alliance A041202-PP1, and Alliance A041202-EL1

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Study Resources:

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Alliance Statistical Data Center
Mayo Clinic
200 First St. SW
Rochester MN 55905

Expedited Adverse Event Reporting
https://eapps-ctep.nci.nih.gov/ctepaers/

Medidata Rave® iMedidata portal
https://login.imedidata.com

OPEN (Oncology Patient Enrollment Network)
https://open.ctsu.org

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Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document:	Protocol Coordinator
Questions related to IRB issues and model consent revisions:	Regulatory Affairs Manager: *regulatory@allianceNCTN.org*
Questions regarding CTEP-AERS reporting:	Pharmacovigilance Inbox *pharmacovigilance@alliancenctn.org*

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**Submit study data:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	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. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	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 CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all 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.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Alliance Study Chair.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) 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.		
The CTSU Web site is located at https://www.ctsu.org.		

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Schema

Patient Eligibility (see Section 4.0 for complete details)

- Diagnosis with CLL in accordance with IWCLL 2008 Criteria
- Intermediate or high risk Rai Stage CLL
- Criteria met for treatment as defined by IWCLL 2008 guidelines
- No prior therapy for CLL (except palliative steroids or treatment of autoimmune complications of CLL with steroids or rituximab)
- Age ≥ 65
- ECOG performance status 0-2
- No active hepatitis B
- No active systemic anticoagulation with heparin or warfarin
- No active intercurrent disease (see Section 4.2.8)
- No history of Richter's transformation or prolymphocytic leukemia
- No prednisone over 20 mg daily or equivalent corticosteroid
- No uncontrolled active system infection requiring intravenous antibiotics
- No strong CYP3A4/5 inhibitors or inducers
- No allergy to mannitol
- No significant hypersensitivity to rituximab
- No major surgery within 10 days or minor surgery within 7 days

Required Initial Laboratory Values

ANC	≥ 1,000/µL *
AST and ALT	≤2.5 x ULN **
Total bilirubin	≤1.5 x ULN ***
Creatinine Clearance	≥ 40 mL/min §
Platelet count	≥ 30,000/µL

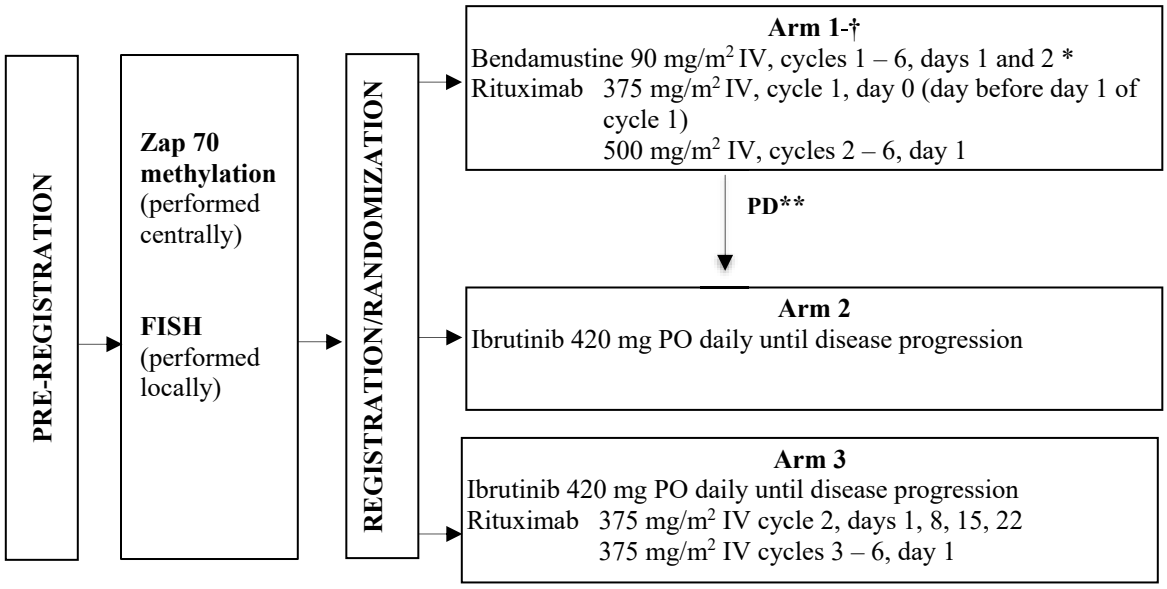
* Unless due to bone marrow involvement

** Except if due to disease infiltration of the liver

*** Unless due to liver involvement, hemolysis or Gilbert's disease

§ To be calculated by modified Cockcroft-Gault formula (see Section 4.2.16).

Schema
1 cycle = 28 days



* At the treating investigator's discretion, the first cycle of bendamustine may be given at 70 mg/m^2.

** Patients randomized to bendamustine plus rituximab will be eligible to cross over to single-agent ibrutinib upon documentation of disease progression. Please note that patients who opt to cross over must be re-registered to the study. In addition, please make sure to reassess eligibility (Section 4.0) at re-registration.

† After completion or discontinuation of treatment on Arm 1, 28-day cycles should continue to be counted as patients will be followed every third cycle.

TABLE OF CONTENTS

1.0 INTRODUCTION

1.1 Initial Therapy for CLL in Older Patients

CLL is the most prevalent form of adult leukemia and is currently incurable. While fludarabine-based chemoimmunotherapy (CIT) is standard initial therapy for younger patients with CLL, optimal initial therapy for older adults with CLL not as well established. Phase III trials have shown that fludarabine is superior to chlorambucil[1] and that fludarabine plus cyclophosphamide is superior to fludarabine[2, 3] or chlorambucil[2] alone. In addition, large phase II and III trials have demonstrated the superiority of chemoimmunotherapy to chemotherapy in this disease.[4, 5] However, all of these studies were heavily skewed toward a younger patient population. A randomized phase III trial[6] has demonstrated that in patients over the age of 65, fludarabine is not superior to chlorambucil. Similarly, a recent analysis of front-line CALGB trials in CLL showed that for patients above the age of 69, fludarabine was not superior to chlorambucil in regards to both PFS and OS. In contrast, the addition of the CD20 monoclonal antibody rituximab to fludarabine improved both PFS and OS over fludarabine alone in both younger patients, and those over the age of 69.[7] Presently, most elderly patients are treated with chlorambucil often in combination with rituximab based on the results of two phase II trials[8, 9] or with the combination of bendamustine plus rituximab (BR). Although BR has not been compared directly with chlorambucil + rituximab, results of a recent phase II trial show an ORR of 88% with a median event free survival of 33.9 months and 90.5% OS at 27 months.[10] These results held for patients ≥ 70 years old, and compare favorably with results published for chlorambucil + rituximab.[10] Toxicity with this regimen is usually manageable but can be significant, with a reported 64% of patients experiencing a grade 3 or grade 4 toxicity, and 19.7% of patients experiencing grade 3 or grade 4 myelosuppression. In older patients especially, these toxicities can delay or preclude further therapy, thus, these results underscore the need for new therapies in the older population who may be particularly at risk for significant toxicity.

1.2 The B Cell Receptor and Bruton's Tyrosine Kinase in CLL

The B cell receptor (BCR) consists of surface immunoglobulin non-covalently bound to the heterodimer CD79a/CD79b. In normal B cells, ligation of the BCR results in a signaling cascade that can lead to proliferation, apoptosis, or anergy depending on the stage of development and antigen ligated.[11] In CLL cells, however, the BCR is dysregulated and activation through antigen ligation or auto-stimulation results in the propagation of proliferative and pro-survival signals.[12, 13] Thus, the BCR represents a therapeutic target in CLL. There are currently two agents clinically available that target different aspects of the BCR in phase III studies: GS-1101 (formerly CAL-101), which is an inhibitor of PI3-kinase p110 delta, and ibrutinib, which inhibits Bruton's Tyrosine Kinase (BTK). BTK is a member of the Tec family of kinases, and is an integral kinase involved in B cell signaling and B lymphocyte development and differentiation. Mutation of the gene encoding BTK, located at Xq21.33-q22 is responsible for X-linked agammaglobulinemia (XLA),[14, 15] a disorder characterized by developmental arrest at the pre-B stage and profound humoral immune deficiency in humans, and the milder X-linked immunodeficiency (XID) phenotype in the mouse.[16] BTK is a crucial mediator of BCR signaling in normal B cells and CLL cells, and is genetically upregulated in CLL as compared to normal B cells.[17] Activation of BTK results in cell survival and proliferation through the MAP kinase pathway, PI3K/Akt pathway, and NF-κB. Because of the key role of BTK in CLL signaling, this is an attractive drug target.

1.3 Targeting BTK with Ibrutinib and Phase I Evaluation

Ibrutinib (PCI-32765) is an orally-bioavailable irreversible inhibitor of BTK. Pharmacologic inhibition of BTK with ibrutinib has been shown to cause modest apoptosis *in vitro*, and significantly inhibits B cell proliferation and signaling both *in vitro* and *in vivo*[17], (and our unpublished data). The initial phase I study with this agent 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.[18] A fluorescent-labeled probe was used to ensure that the doses brought forward occupied >90% of BTK.[19] Based on this study, an oral dose of 420 mg daily was established as a tolerable and effective dose. The drug was well tolerated at all dose levels examined, with only 5 out of 47 patients discontinuing therapy for toxicity.[18]

1.4 Phase II Study of Ibrutinib in CLL

In an ongoing phase Ib/II study, ibrutinib has shown extraordinary activity in patients with relapsed or refractory CLL. In patients with relapsed or refractory CLL and measurable lymphadenopathy, the rate of lymph node shrinkage >50% is 89%. With a median follow-up of 4 months, ORR was 48% due to transient asymptomatic lymphocytosis[20], and with longer follow-up of 17.3 months in patients receiving the 420 mg dose, has improved to 67%.[21] This lymphocytosis has been observed in clinical trials with the PI3kinase delta inhibitor GS-1101 as well and is likely related to B cell release from lymph node, spleen and marrow microenvironment due to disruption of homing signals or chemoattractants that are relevant to usual lymphocyte circulation dynamics. Lymphocytosis with ibrutinib is seen within 1-2 weeks of starting therapy, reaches plateau within the first 2-3 cycles, 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 occurs independently of high-risk genomic features including IgVH mutational status and del(17p13.1). Responses to this drug have been durable as well, with an estimated 22 month PFS of 76% for these relapsed and refractory patients.[21] This study also included a cohort of 31 previously untreated patients. With 16.6 months of follow-up, ORR is 71%, with an additional 10% of patients having persistent lymphocytosis; estimated 22 month PFS is 96%.[21] Thus far only 7 out of 116 patients across treatment cohorts have been removed from study for disease progression. This oral agent is well tolerated, with a very low rate of hematologic toxicity. The most common toxicities with ibrutinib have been diarrhea, rash, bruising, and dyspepsia. There has been no change in the levels of IgG and IgM, and an increase in serum IgA has been seen over time.[21]

Infections, including opportunistic infections have been observed, however, infections are common in this refractory patient population. Serious infectious AEs have been experienced by 20 patients in this relapsed/refractory group, but in general have not led to discontinuation of therapy. The efficacy observed thus far in conjunction with the tolerability to continuous administration make it an ideal agent for further study, especially in elderly patients.

In line with all other trials currently including ibrutinib, patients on this trial will adhere to a continuous dosing regimen of this agent until disease progression. This model of continuous therapy is based on kinase inhibition in chronic myelogenous leukemia (CML) with imatinib, and at this point appears reasonable given the relatively large number of patients who achieve only partial response and continue to have improving response with longer duration of ibrutinib administration. If, within the duration of this trial, evidence arises suggesting that all or some patients would do well with therapy discontinuation or interruption, this protocol will be amended to reflect this change. Until this time, however, patients treated on this protocol are expected to receive continuous dosing of ibrutinib until disease progression.

1.5 Combination Therapy

Combination Therapy with CD20 Monoclonal Antibody Therapy and Ibrutinib

The combination of ibrutinib with a CD20 monoclonal antibody is appealing because the rapid clearing of peripheral lymphocytosis that is seen with rituximab and other antibodies is expected to increase the rapidity of response with ibrutinib. Additionally, in the laboratory ibrutinib antagonizes the tumor microenvironment,[17] which may increase the bone marrow clearance which is limited with rituximab. The combination of ibrutinib and the CD20 monoclonal antibodies ofatumumab or rituximab are currently being evaluated in relapsed CLL on two separate trials. One, a phase II study of ibrutinib (420 mg) administered continuously until time of relapse and ofatumumab has enrolled three time-sequential cohorts. In the first cohort of 27 patients, ibrutinib begins day 1 and continues until disease progression, while ofatumumab begins month 2 with 300 mg week 5, 2000 mg weeks 6-12 and then monthly for four months. All 27 patients completed the first month of therapy without a DLT. Of the twenty-four patients with CLL, all attained a partial response (100%) with 23 remaining on treatment and 1 proceeding to a non-myeloablative stem cell transplant. Infusion toxicities with ofatumumab were more modest than expected. Cohorts administering ofatumumab either concurrently or prior to ibrutinib have also been completed where feasibility was confirmed, but either early toxicity (concurrent schedule) or early progression (ofatumumab first arm) has resulted in choosing the run in arm with ibrutinib for 1 month followed by addition of ofatumumab for future study. In the other trial performed at MD Anderson which enrolled only patients with high-risk disease, rituximab and ibrutinib were administered concurrently beginning in cycle 1, with 4 doses of weekly rituximab and then monthly administration for a total of 6 cycles. In this trial, toxicities were modest, and responses were again seen at an earlier time point than expected from single agent therapy.[22] Overall, experience with different administration sequences suggests that a run in with ibrutinib for the first month followed by initiation of antibody beginning month two may be better tolerated, and *in vivo* pharmacodynamic studies support target modulation that would enhance tumor apoptosis. This schedule of administration with ibrutinib preceding CD20 antibody therapy will be pursued in this phase III trial.

1.6 Clinical Safety Update 2015

Pooled safety data are available for a total of 1071 patients treated with ibrutinib monotherapy across 9 studies in B-cell malignancies, including patients from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy (Investigator's Brochure, 2015). The most frequent treatment-emergent AEs (TEAEs) are summarized below.

Ibrutinib Monotherapy Studies (N=1071)		
Most frequently reported TEAEs (>15%)	**Most frequently reported Grade 3 or 4 TEAEs (>2%)**	**Most frequently reported Serious TEAEs (>2%)**
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
Pyrexia	Atrial fibrillation	
Neutropenia	Diarrhea	
	Febrile neutropenia	
	Hyponatremia	

TEAE = treatment-emergent adverse event

For more detailed information, refer to the current version of the Investigator's Brochure.

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.

1.7 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/μL) may confer increased risk.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (*i.e.*, ≥50% increase from baseline and an absolute count >5000/μL), 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/mcL) 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.

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.

1.8 Justification

Justification for a Phase III Trial of Ibrutinib and Ibrutinib plus Rituximab versus BR in CLL

The excellent response rates and durable remissions seen thus far with ibrutinib, especially in comparison to modest outcomes and significant toxicity with standard therapy in this age group, justify the movement to phase III study as initial therapy for older patients with CLL. We therefore will perform a phase III trial of bendamustine plus rituximab versus ibrutinib versus ibrutinib plus rituximab to determine whether ibrutinib containing regimens are superior to standard therapy and also to determine whether combination therapy with ibrutinib plus rituximab is superior to ibrutinib alone. Rituximab is chosen as the CD20 antibody as it is currently being approved for CLL in combination with fludarabine and cyclophosphamide for CLL and also because of its common use with bendamustine in both previously treated and recently untreated CLL. This study will include patients aged 65 and older with untreated CLL in need of therapy. The primary endpoint will be PFS, which is an appropriate endpoint in an indolent disease with multiple options for second-line therapy, especially in an older population with competing risk factors for death. We expect that this trial will show that regimens containing ibrutinib are superior to standard therapy and thus will be practice changing and will transform initial therapy in this disease. Additionally, correlative laboratory samples obtained through this trial will allow detailed mechanistic studies into the biology associated with this agent.

Justification for correlative studies

The high response rates and durable remissions that have been seen with ibrutinib alone and in combination in early phase trials have limited the ability to draw conclusions regarding prognostic factors with this agent. Similarly, no data is available on resistance to or relapse after ibrutinib, both factors that predict resistance/relapse or relapse phenotypes. Therefore, a large phase III trial has the opportunity to impact the field both with novel therapies and detailed correlative analyses that may be applicable to both this drug and other kinase inhibitors. Since the cytogenetic abnormalities of del(17p13.1) and del(11q22.3) have been shown to be such strong biomarkers with other CLL therapies, and because there is a suggestion from ongoing trials that response may be improved in patients without Zap-70 methylation at CpG3, randomization will be stratified based on these factors as well as disease stage. Correlative biomarker studies will be required for all trial participants, as they are factors in randomization and interpretation of results. In addition, we will evaluate traditional biomarkers that predict response and response duration with chemoimmunotherapy, including stimulated cytogenetics (or equivalent), FISH, IgVH mutational status, Zap-70 methylation, baseline miR and gene expression profiling. Furthermore, novel recurrent DNA mutations have been identified in a significant subset of CLL patients and have been shown to be potential biomarkers of disease natural history; we will evaluate these in patients treated with standard therapy as well as ibrutinib containing regimens. Finally, studies derived from relapsed samples in each arm will be assessed for mutations and other biochemical features associated with resistance to ibrutinib

Identification of patient groups that respond to ibrutinib monotherapy without the need for additional therapy is of great interest. In this regard, it has been identified that serial changes in miRs demonstrated 10 that were variably modulated at day 29 of ibrutinib. Of prime importance was down-regulation of miR-155, which has been associated with poor prognosis in CLL.[23] The expression of miR-155 is positively regulated by NF-κB,[24] which is inhibited by ibrutinib. Similarly, miR-29c has been identified as having reduced expression in progressive CLL[23] and in del(17p13.1) disease[25] and ibrutinib treatment increases this miR. Additionally, low

miR-155 and high miR-29c was associated with ZAP-70 methylated disease and also favorable outcome in two CALGB chemoimmunotherapy studies. These miRs and other plasma or cellular markers as potential early biomarkers of response will be pursued as part of this study in the two ibrutinib arms. It is hoped that these early biomarkers will assist in identifying CLL patients who gain extended benefit to ibrutinib monotherapy.

The eradication of minimal residual disease has been shown with chemoimmunotherapy to identify a subset of patients with prolonged remission duration and potentially improved survival. Previous studies with kinase inhibitors have not addressed the impact of MRD or MRD eradication on response duration, so this will be evaluated in the context of this trial at 9 months and 24 months. This will be done centrally as part of bone marrow assessment of disease using 4-color high sensitivity flow cytometry.

1.9 Registration Quality of Life (QOL) Measurements

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates.[26, 27]

2.0 OBJECTIVES

2.1 Primary Objective

To determine whether progression free survival (PFS) is superior after therapy with bendamustine in combination with rituximab, ibrutinib alone, or ibrutinib in combination with rituximab in patients age 65 or older with previously untreated CLL

2.2 Secondary Objectives

2.2.1 To determine 2-year PFS in each of the three treatment arms

2.2.2 To determine which treatment arm produces superior overall survival (OS)

2.2.3 To determine the complete response (CR) rate, complete and nodular partial response (CR/nPR) rate, and overall response (PR+nPR+CR) rate (ORR) among the three treatment arms and compare these arms

2.2.4 To determine the impact of MRD-negative disease at time of CR documentation and at 2 years on PFS and OS in each of the treatment arms

2.2.5 To determine duration of response after each of the three treatments and compare these treatment arms

2.2.6 To determine toxicity and tolerability of the three treatment regimens

2.2.7 To determine response and PFS of patients initially on the bendamustine in combination with rituximab arm who cross over to ibrutinib

2.2.8 To determine whether baseline cytogenetic markers, Zap-70 methylation, IgVH mutational status, or select DNA mutations predict outcomes or time to response in these three arms

2.2.9 To determine whether local FISH results for del(11q22.3) and del(17p13.1) are consistent with central analysis.

2.2.10 To determine whether baseline microRNA and gene expression markers are correlated with clinical outcomes of interest (e.g. progression-free and alive at 2 years versus not), as well as to explore changes in microRNA expression from baseline to post-treatment time points, with a focus on those with persistent lymphocytosis and relapse

2.2.11 To determine whether eradication of MRD predicts longer duration of response with standard therapy and ibrutinib-based regimens

2.2.12 To describe the baseline functional status, comorbid medical conditions, and number of medications of older CLL patients who meet criteria for therapy

2.2.13 To determine how functional status changes with therapy using baseline to 3-month evaluation and end-of-study/2-year evaluation; to determine whether this change is different among the treatment groups

2.2.14 To determine whether geriatric assessment variables known to be associated with chemotherapy toxicity in other disease groups can also predict therapy-associated toxicity in the CLL population

2.2.15 To assess whether the *FCGR3A* polymorphism (rs396991) is correlated with depth of response (MRD status) to ibrutinib plus rituximab after 6 cycles, with secondary endpoints CR rate, rapidity of response, and progression-free survival (PFS)

2.2.16 To assess whether *C1QA* polymorphism (rs172378) is correlated with MRD status, CR rate, rapidity of response, and PFS

3.0 ON-STUDY GUIDELINES

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate. Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness, which would prevent the patient from giving informed consent
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient
- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study and for 90 days after the last dose of study drug due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives, or double barrier method (diaphragm plus condom).
- Patients who are unable to swallow solid oral dosage forms will not be able to take the study treatment drugs.
- Patients may not have an active intercurrent disease or concurrent malignancy that is expected to limit survival to < 5 years.

- Patients requiring other anticoagulants or medications that inhibit platelet function should use ibrutinib with caution. Ibrutinib use in patients with congenital bleeding diathesis has not been studied. Please see Section 11.2 for the specific anticoagulation therapies that must be avoided.

4.0 ELIGIBILITY CRITERIA

All questions regarding eligibility criteria should be directed to the Alliance Study Chair. Please note that the Study Chair cannot grant waivers to eligibility requirements.

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

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

4.1 Pre-Registration Eligibility Criteria (Step 0)

4.1.1 Central Zap-70 submission

All patients are REQUIRED to be pre-registered to A041202 in order to submit peripheral blood to the Alliance Hematologic Malignancy Biorepository (HEME) for central Zap-70 methylation (See Section 6.2.1). This specimen submission is mandatory prior to registration as results will be used for stratification. See Section 6.2 for details on specimen submission.

4.2 Registration Eligibility Criteria (Step 1)

4.2.1 Documentation of Disease:

Patients must be diagnosed with CLL in accordance with IWCLL 2008 criteria[28] that includes all of the following:

- $\geq 5x10^9$ B lymphocytes (5000/μL) in the peripheral blood
- On morphologic review, the leukemic cells must be small mature lymphocytes, and prolymphocytes must not exceed 55% of the blood lymphocytes.
- CLL cells on immunophenotype (performed locally) must reveal a clonal B-cell population, which express the B cell surface markers of CD19 and CD20, as well as the T-cell antigen CD5. Patients with bright surface immunoglobulin expression or lack of CD23 expression in >10% of cells must lack t(11;14) translocation by interphase cytogenetics.

4.2.2 Staging and Indication for Therapy

- Patients must be intermediate or high-risk Rai stage CLL.
  - Intermediate risk (formerly Rai stage I/II) is defined by lymphocytosis plus enlarged lymph nodes at any site, with or without hepatomegaly or splenomegaly
  - High risk (formerly Rai stage III/IV) is defined by lymphocytosis with or without enlarged nodes and spleen plus disease-related anemia (hemoglobin <11 g/dL) or thrombocytopenia (platelet count $<100 \times 10^9$/L) that is not attributable to autoimmune hemolytic anemia or thrombocytopenia

- Patients must meet criteria for treatment as defined by IWCLL 2008 guidelines[28] which includes at least one of the following criteria:
    - Evidence of marrow failure as manifested by the development or worsening of anemia or thrombocytopenia (not attributable to autoimmune hemolytic anemia or thrombocytopenia)
    - Massive (≥6 cm below the costal margin), progressive or symptomatic splenomegaly
    - Massive nodes (≥10 cm) or progressive or symptomatic lymphadenopathy
    - Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy
    - Constitutional symptoms, which include any of the following:
        - Unintentional weight loss of 10% or more within 6 months
        - Significant fatigue
        - Fevers >100.5 degrees F for 2 weeks or more without evidence of infection
        - Night sweats >1 month without evidence of infection

4.2.3 Prior Treatment

- Patients must not have had prior therapy for CLL (except palliative steroids or treatment of autoimmune complications of CLL with rituximab or steroids).
- Treatment with rituximab and/or high dose corticosteroids for autoimmune complications of CLL must be complete at least 4 weeks prior to enrollment. Palliative steroids must be at a dose not higher than 20 mg/day of prednisone or equivalent corticosteroid at the time of registration.

4.2.4 Age ≥ 65 years

4.2.5 ECOG Performance Status 0-2

4.2.6 Active Hepatitis B

Patients with active hepatitis B defined by hepatitis B surface antigen positivity or core antibody positivity in the presence of hepatitis B DNA are not eligible for this study. Patients with a positive hepatitis B core antibody but with negative hepatitis B DNA may participate, but must have hepatitis serologies and hepatitis B DNA monitored periodically by the treating physician.

IVIG can cause a false positive hepatitis B serology. If patients receiving routine IVIG have core antibody or surface antigen positivity without evidence of active viremia (negative hepatitis B DNA) they may still participate in the study, but should have hepatitis serologies and hepatitis B DNA monitored periodically by the treating physician.

4.2.7 Active systemic anticoagulation

Patients must not be receiving active systemic anticoagulation with heparin or warfarin. Patients must be off warfarin therapy for at least 30 days prior to enrollment.

4.2.8 Active intercurrent disease

Patients with Class III or Class IV heart failure by New York Heart Association, those with unstable angina, and those with uncontrolled arrhythmia are not eligible.

Patients who have had a myocardial infarction, intracranial bleed, or stroke within the past 6 months are not eligible.

Patients with known HIV are eligible if their CD4 count is ≥ 350 cells/mm3 and if they are not taking prohibited CYP-interacting medications (See Section 4.2.12).

4.2.9 Richter's transformation or prolymphocytic leukemia

Patients must not have any history of Richter's transformation or prolymphocytic leukemia (prolymphocytes in blood > 55%).

4.2.10 Prednisone or equivalent corticosteroid

Patients must not require more than 20 mg prednisone or equivalent corticosteroid daily.

4.2.11 Intravenous antibiotics

Patients must not have uncontrolled active systemic infection requiring intravenous antibiotics.

4.2.12 CYP3A4/5 inhibitor or inducer

Patients must not have continued requirement for therapy with a strong CYP3A4/5 inhibitor or inducer (See Appendix II).

4.2.13 Allergy to mannitol

Patients must not have a known allergy to mannitol.

4.2.14 Significant hypersensitivity to rituximab

Patients must not have prior significant hypersensitivity to rituximab (not including infusion reactions).

4.2.15 Prior Surgery

Patients may not have had major surgery within 10 days of enrollment, or minor surgery within 7 days of enrollment. Examples of minor surgery include dental surgery, insertion of a venous access device, skin biopsy, or aspiration of a joint. The decision about whether a surgery is major or minor can be made at the discretion of the treating physician.

4.2.16 Initial laboratory values

Patients must meet the following required initial laboratory values:

ANC	≥ 1,000/μL unless due to bone marrow involvement
AST or ALT	≤ 2.5 x upper limits of normal except if due to disease infiltration of the liver
Bilirubin	≤ 1.5 x upper limits of normal (unless due to liver involvement, hemolysis, or Gilbert's disease)
Creatinine Clearance	≥ 40 mL/min*
Platelet count (untransfused)	≥ 30,000/μL

* To be calculated by modified Cockcroft-Gault formula as follows:

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age in years}) \times \text{actual wt (in kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad \times .85 \text{ (for female patients)}$$

5.0 REGISTRATION/RANDOMIZATION, STRATIFICATION

5.1 Pre-registration Requirements (Step 0)

5.1.1 Informed Consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Human subject protection committee approval of this protocol and a consent form is required.

5.1.2 Zap-70 Methylation

All patients are REQUIRED to be pre-registered to A041202 in order to submit peripheral blood to the Alliance Hematologic Malignancy Biorepository (HEME) for central Zap-70 methylation prior to registration (see Section 6.2.1). Within 10 days of receipt of the specimen, the treating physician/institutional contact will be notified of the results, which must be documented on the patient enrollment form. Results of Zap-70 are needed for patient registration, and patients must register to A041202 within 14 days of notification of Zap-70 results. Zap-70 results are only used for stratification purposes and DO NOT determine patient eligibility.

5.2 Registration Requirements (Step 1)

5.2.1 FISH must be performed locally within 30 days prior to registration (see Section 6.2.1). Registration must occur within 14 days of notification of Zap-70 results and prior to the initiation of therapy. Rai stage at screening by Zap-70, as well as status of del(11q22.3) and del(17p13.1) by FISH, must be documented on registration form. After patient registration, the institutional contact will receive a registration confirmation and treatment confirmation, which includes the randomization arm.

5.2.2 Registration to the required laboratory correlative science (A041202-LC1), optional pharmacogenetic (A041202-PP1), and optional geriatric functional status assessment (A041202-EL1) correlative studies will be performed at the time registration occurs to the treatment study. Patients should not be enrolled on the A041202-EL1 correlative study until institutional staff have been trained (see Section 5.4.2). See Section 5.4 for correlative science registration procedures.

5.3 Registration Procedures

5.3.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR Help Desk by email at < RCRHelpDesk@nih.gov >.

5.3.2 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. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the A041202 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
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol #A041202
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for A041202 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- For applicable NCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.

Submitting Regulatory Documents:

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

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab

→Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- 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
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

5.3.3 OPEN Access Requirements and Procedures

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 in the Rave 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 have 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 pre-registration, registration and treatment information. Please print this confirmation for your records.

To receive site reimbursement for patient participation in A041202-PP1 or A041202-EL1, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

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.

5.4 Registration to Correlative Science Studies and Companion Protocols

5.4.1 Registration to Correlative Studies Described in Section 10.0

There are three embedded correlative science companion studies within Alliance A041202. **A041202-LC1 pertaining to correlative studies is essential for interpretation of the trial results and is therefore mandatory**. A041202-PP1 and A041202-EL1 **must be offered to all patients** enrolled on Alliance A041202 (although patients may opt to not participate). These correlative science companion studies do not require separate IRB approval. The correlative science companion studies included within Alliance A041202 are:

- Leukemia Correlative Science in Alliance A041202 (A041202-LC1, Section 10.1)
- Geriatric Assessment in Alliance A041202 (A041202-EL1 Section 10.2)

  Geriatric Assessment questionnaire booklets for A041202-EL1 are to be ordered prior to the registration of any patients. For booklet ordering instructions see Section 6.3.
- Evaluation of Candidate Pharmacogenetic Determinants of Ibrutinib or Ibrutinib/Rituximab Response (A041202-PP1, Section 10.3)

5.4.2 Site Credentialing for Companion Study A041202-EL1

At least one member of the research team at each participating institution must complete a brief training on the geriatric assessment procedures before enrolling any patients to this companion study. If multiple individuals are responsible for administering the Geriatric Assessment, each of these individuals must complete the training. The training module may be accessed on the member side of the Alliance website (www.allianceforclinicaltrialsinoncology.org). In order to gain access to the member side of the Alliance website, the user must have an active CTEP-IAM account that is linked to at least one of the NCTN group rosters. To login, select "Member Login" on the Alliance homepage and enter the CTEP-IAM account username and password. After logging in, the training module can be found under education and training > online training and under "For Site Staff." Once the training is complete, print a copy of the completion certificate to keep in study records.

If you have difficulties accessing or completing the online training, contact that the A041202 Protocol Coordinator, so that a training may be coordinated via telephone. Retain email documentation from the study team that states that the training was completed.

5.4.3 Registration to Companion Protocol (Temporarily Suspended as of February 28, 2014)

There is one optional separate companion protocol associated with Alliance A041202, CALGB 9665: The CALGB Leukemia Tissue Bank. However, CALGB 9665 was temporarily suspended on February 28, 2014. Therefore, after February 28, 2014, Alliance institutions may not consent or enroll patients on CALGB 9665. Patients already enrolled on CALGB 9665 should continue to submit specimens as required.

Refer to the CALGB 9665 protocol document for specimen procurement and submission instructions. The time points for specimen submission, outlined within CALGB 9665 (as well as Section 6.2.1), are:

- At time of diagnosis/registration: Bone marrow aspirate, peripheral blood, buccal cell sample (saliva). Buccal cell sample is collected at diagnosis/registration for A041202-LC1, and on day 1 of cycle 1 for CALGB 9665.
- Relapse/Progression: Bone marrow aspirate, peripheral blood
- During remission: Bone marrow aspirate, peripheral blood

5.5 Stratification

Stratification on A041202 will be according to Rai stage (intermediate versus high), presence or absence of del(11q22.3) or del(17p13.1) on FISH (performed by individual institutions), and < versus ≥ 20% methylation of CpG 3 on Zap-70 (performed centrally). In the event that a sample does not yield a Zap-70 methylation status, data will be input based on IgVH mutational status as follows: >20 if IgVH mutated or <20 for unmutated.

5.6 Re-Registration at the Time of Progression

Patients randomized to bendamustine plus rituximab (Arm 1) will be eligible to cross over to single-agent ibrutinib upon documentation of disease progression. Please note that patients who opt to cross over must be re-registered to the study within 12 months of progression documentation. The delay is only to allow for patients who do not immediately require additional therapy at the time of progression. Intervening treatment for CLL prior to crossover is not permitted. In addition, please make sure to reassess eligibility (Section 4.0) at re-registration. Patients do NOT need to meet eligibility requirement of $5x10^9$ B lymphocytes in the peripheral blood. See Section 7.0 for required tests and observations to be completed prior to re-registration. Please note that even though patients are crossing over to Arm 2, the registration system will refer to the re-registration arm assignment as "Arm 4." Patients who crossover to single agent ibrutinib should restart the study calendar after re-registration (i.e. the first day of ibrutinib would be considered Day 1 of Cycle 1). Follow the study calendar (Section 7.0) and specimen submission schedule (Section 6.2.1) as required for patients assigned to Arm 2 (unless specifically stated otherwise).

Re-registration procedures:

OPEN may be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU website at https://www.ctsu.org, or from the OPEN Registration tab on the CALGB website.

To enroll a patient within OPEN, institution staff must have:

1. A valid and active CTEP-IAM account. This is the same user ID and password used for CTSU's website (for more information see https://www.ctsu.org/public/CTEP-IAM_Factsheet.pdf).
2. Enrollment of patients on CALGB coordinated protocols requires a "Registrar" role in the CALGB roster. Assignment of the "Registrar" role is managed through the CALGB Central Office via submission of a roster update form signed by the Principal Investigator of the member network.

The OPEN system will provide the registering site with a printable confirmation of re-registration. Please print the confirmation for your records. Further instructional information is provided on the CTSU members' website OPEN tab, or within the OPEN URL. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923, or ctsucontact@westat.com.

6.0 DATA AND SAMPLE SUBMISSION

6.1 Data Submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. 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/index.jsp >) 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 a 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 on 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 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 members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

6.1.1 Data Submission Schedule and Requirements

A Data Submission Schedule is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

Please note that cycles are 28 days (this applies to both treatment and follow-up). Beginning with Day 1 of Cycle 6, patients are only required to be seen every 3 cycles. Sites may choose to enter data into Rave in either 28 or 84 day cycles. The visit number in Rave will not match the treatment cycle # unless 28 day cycles are chosen in Rave after Day 1 of Cycle 6.

Please contact the Data Manager listed on the protocol cover page for data submission questions.

6.1.2 Adverse Event Data Submission

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for routine toxicity and adverse event (AE) reporting. Please note that AE reporting stops at discontinuation of protocol therapy. **Note:** CTCAE version 5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018 (see Section 16.1).

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. Section 16.0 provides information about expedited reporting.

Solicited Adverse Events: The following abnormalities/adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment for the first six months on study. After six cycles of treatment, patients who continue to receive ibrutinib on Arms 2 and 3 should submit solicited AEs every 3 months.

- Neutrophil count decreased (see Investigations in CTCAE v.4)
- Platelet count decreased (see Investigations in CTCAE v.4)
- Infusion related reaction (see General disorders and administration site conditions in CTCAE v.4)

- Anaphylaxis (see Immune system disorders in CTCAE v.4)
- Allergic reaction (see Immune system disorders in CTCAE v.4)
- Tumor lysis syndrome (see Metabolism and nutrition disorders in CTCAE v.4)
- Rash maculo-papular
- Fatigue
- Cough
- Diarrhea
- Edema limbs (see General disorders and administration site conditions in CTCAE v.4)
- Dizziness
- Dyspepsia
- Anemia
- Hypertension
- Bruising

6.2 Specimen Collection & Submission

Specimens for patients registered on Alliance A041202 and its substudies must be logged and shipped using the online Alliance Biospecimen Management System (BioMS).

All submitted specimens must be labeled with the protocol number (A041202), patient ID number, patient's initials, and date and type of specimen collected (e.g., serum, whole blood).

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.wustl.edu/bioms, using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

6.2.1 Specimen Submission Overview

Specimen	Baseline*	Day 1, Cycle 1	Day 1, Cycle 2**	Day 1, Cycle 9	Day 1, Cycle 27 ***	Remission	Progression	Ship to:
For ALL patients registered to A041202, submit the following:								
Central morphology review	6 bone marrow smears, 6 blood smears, 2 biopsy sections; and if dry tap, 2 marrow touch preps (see 6.2.2)							OSU
Bone marrow aspirate	1 x 10 mL EDTA tube			1 x 10 mL EDTA tube	1x10 mL EDTA tube		1 x 10 mL EDTA tube	HEME
Peripheral whole blood	4x10 mL acid citrate dextrose (ACD) tubes, 1x 5 mL heparin tube, 1 x 5 mL EDTA tube§		4x10 mL ACD tubes	4x10 mL ACD tubes	4x10 mL ACD tubes		4x10 mL ACD tubes, 1x10 mL heparin tube	HEME
Buccal cell sample	50 mL sterile tube							HEME
For patients registered to CALGB 9665[A], submit the following:								
Bone marrow aspirate	5 mL in 1 or 2 lavender top tubes					5 mL in 1 or 2 lavender top tubes	5 mL in 1 or 2 lavender top tubes	HEME
Peripheral whole blood	10 mL in 2 – 3 lavender top tubes					10 mL in 2 – 3 lavender top tubes	10 mL in 2 – 3 lavender top tubes	HEME
Buccal cell sample		50 mL sterile tube						HEME
For patients registered to A041202-PP1[B], submit the following:								
Peripheral whole blood	2 x 5 mL EDTA tubes							HEME
Bone marrow aspirate	1 mL in 1 EDTA tube							HEME

* Baseline samples (except the EDTA tube that must be submitted for Zap-70 methylation) may be sent at any point from the date of pre-registration, but must be sent prior to the initiation of therapy.

** Arm 2 and arm 3 only

*** Required for all patients except those on Arm 1 who have crossed over to receive ibrutinib. Patients who have crossed over to ibrutinib should restart specimen collection beginning on Day 1 of Cycle 2 of ibrutinib.

§ EDTA tube must be submitted at pre-registration (for Zap-70 Methylation).

A Collect and submit only from patients who enrolled on CALGB 9665 prior to the temporary suspension on February 28, 2014.

B Collect and submit only from patients who consent to model consent question #2.

All patients must have FISH for del(17p13.1) and del(11q22.3) performed locally within 30 days of registration, which will be used for stratification. FISH results must be documented on the OPEN enrollment form at registration. Additionally, a copy of the original forms of the FISH results must be submitted via Medidata Rave.

All patients will undergo Zap-70 methylation centrally prior to randomization. Collect and submit the 1 x 5 mL EDTA tube at pre-registration for Zap-70 methylation (see Section 6.2.4.2). Within 10 days of receipt of the specimens, the treating physician/institutional contact will be notified of the results, which must be documented on the OPEN enrollment form at registration. Upon patient registration, the institution will be sent a registration confirmation, as well as the randomization arm.

For patients who have undergone a bone marrow procedure prior to patient consent/pre-registration, enrollment may be permitted provided Study Chair approval is obtained via e-mail and documented in the patient's charts. In this case, baseline bone marrow LC1 specimens are not required, but material will need to be submitted for central morphology review.

6.2.2 Central Morphology Review

6.2.2.1 Prior to initiation of therapy, obtain (6) air-dried, unstained bone marrow smears (films) and six (6) unstained blood smears (films) for confirmatory cytologic and cytochemical studies. These should be sent to the Alliance Biorepository at Ohio State University (OSU) immediately at the address below, following instructions in Section 6.2.2.4.

6.2.2.2 Also submit: 1) two unstained bone marrow biopsy sections; and 2) two unstained marrow biopsy touch preparations if the aspirate was a dry tap.

6.2.2.3 All specimens required for participation on A041202 should take priority over other specimens collected, regardless of site or group affiliation. Send the bone marrow biopsy smears and films plus core and touch prep unstained slides to the Alliance Biorepository at OSU. Send via overnight traceable courier service, no Saturday shipments should be included.

6.2.2.4 Label each slide with the patient's Alliance ID number obtained through pre-registration and protocol number (A041202). Pack carefully in protective slide cartons (not cardboard folders). Samples must be logged and shipped via the BioMS see Section 6.2 for instructions. A copy of the shipping manifest produced by the BioMS must be printed and placed in the shipment with the specimens. Promptly mail (slides must arrive within one week of sampling) to:

Alliance Biorepository at Ohio State University (OSU)
Department of Pathology
Polaris Innovation Centre
2001 Polaris Parkway
Columbus, OH 43240
Tel: 614-293-7073
Fax: 614-293-7967
path.calgb@osumc.edu

Send a copy of your institutional bone marrow aspiration and biopsy report, CBC report, and immunophenotyping report as soon as complete to the Biorepository at OSU. These reports must include differential cell counts and cytochemistry results.

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery" and "Priority Overnight Service". Do not ship specimens on Saturdays. Please be sure to use a method of shipping that is secure and traceable.

6.2.3 Specimen Submission for Correlative Protocol: CALGB 9665

CALGB 9665 was temporarily suspended on February 28, 2014. Therefore, after February 28, 2014, Alliance institutions may not consent or enroll patients on CALGB 9665. Patients already enrolled on CALGB 9665 should continue to submit specimens. Refer to the CALGB 9665 protocol document for specimen submission. The specimens to be submitted for CALGB 9665 are also included in the specimen submission table below. CALGB 9665 is open to Alliance institutions only.

6.2.4 Specimen Submission for Correlative Studies Alliance A041202-LC1 and Alliance A041202-PP1

6.2.4.1 Bone Marrow Submission (Alliance A041202-LC1) (For all patients)

From all patients, collect 10 mL of bone marrow aspirate at baseline, day 1 of cycle 9, at month 24, and at time of disease progression in an EDTA tube.

Specimens for patients registered on this study must be logged and shipped using the online Alliance BioMS, as described in Section 6.2.

The specimens should be labeled with the study number (A041202), Alliance patient ID, patient's initials, institution, and date and time of specimen procurement, and sample type. A copy of the shipping manifest produced by the BioMS must be printed and placed in the shipment with the specimens. Specimens should be sent at ambient temperature on the same day as collection to the Alliance Hematologic Malignancy Biorepository (HEME):

Alliance Hematologic Malignancy Biorepository
The Arthur G. James Cancer Hospital and Research Institute
300 West 10th Avenue, Lobby
Columbus, OH 43210
Tel: 614-688-4754 Fax: 614-688-4755

Ship specimens by overnight courier to the Alliance Hematologic Malignancy Biorepository the same day they are collected. Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays or Sundays. Please be sure to use a method of shipping that is secure and traceable.

6.2.4.2 Peripheral Blood Submission (Alliance A041202-LC1) (For all patients)

From all patients, collect peripheral blood samples at baseline, day 1 of cycle 2 (for patients on arm 2 and arm 3 only), day 1 of cycle 9, at month 24, and at progression. The amounts collected and appropriate tubes for each time point are outlined above in the table in Section 6.2.1.

Specimens for patients registered on this study must be logged and shipped using the online Alliance BioMS, as described in Section 6.2..

The specimens should be labeled with the study number (A041202), Alliance patient ID, patient's initials, institution, and date and time of specimen procurement, and sample type. A copy of the shipping manifest produced by the BioMS must be printed and placed in the shipment with the specimens and sent to the Alliance Hematologic Malignancy Biorepository. Specimens should be sent at ambient temperature on the same day as collection to the Alliance Hematologic Malignancy Biorepository (HEME):

Alliance Hematologic Malignancy Biorepository
The Arthur G. James Cancer Hospital and Research Institute
300 West 10th Avenue, Lobby
Columbus, OH 43210
Tel: 614-688-4754 Fax: 614-688-4755

Ship specimens by overnight courier to the Alliance Hematologic Malignancy Biorepository the same day they are collected. Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays. Please be sure to use a method of shipping that is secure and traceable.

6.2.4.3 Buccal Cell Sample Submission (Alliance A041202-LC1) (For all patients)

One buccal cell sample should be obtained from each patient at baseline. As noted in Section 6.2.1, patients who enrolled on CALGB 9665 prior to February 28, 2014 will have an additional sample collected on cycle 1 day 1. **Buccal collection kits may be obtained by contacting the Alliance HEME Biorepository at 614-688-4754.** In the event that you need to collect a sample but don't have a kit, have patient rinse mouth with 10mL of mouth wash (e.g. Scope) for 30 to 60 seconds, and then spit the mouthwash back into a 50 mL sterile tube. Securely tighten the cap on the tube and label the tube with the patient ID and date of specimen collection. Place the tube in a biohazard bag and seal the bag. Keep any samples refrigerated until you are ready to ship. The buccal cell sample must be collected before brushing teeth or at least 2 hours after brushing teeth, eating or drinking. This specimen may be collected at any time before starting protocol therapy. Buccal cell samples for A041202-LC1 and CALGB 9665 should not be collected on the same day. The buccal cell specimen should be submitted the same day as collected.

Specimens for patients registered on this study must be logged and shipped using the online Alliance BioMS, as described in Section 6.2.

The specimens should be labeled with the study number (A041202), Alliance patient ID, patient's initials, institution, and date and time of specimen procurement, and sample type. A copy of the shipping manifest produced by the BioMS must be printed and placed in the shipment with the specimens and sent to the Alliance Hematologic Malignancy Biorepository. Specimens should be sent at ambient temperature on the same day as collection to the Alliance Hematologic Malignancy Biorepository (HEME):

Alliance Hematologic Malignancy Biorepository
The Arthur G. James Cancer Hospital and Research Institute
300 West 10th Avenue, Lobby
Columbus, OH 43210
Tel: 614-688-4754 Fax: 614-688-4755

Ship specimens by overnight courier to the Alliance Hematologic Malignancy Biorepository the same day they are collected. Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays. Please be sure to use a method of shipping that is secure and traceable.

6.2.4.4 Bone Marrow Aspirate and Whole Blood Submission (Alliance A041202-PP1)

One mL of the initial bone marrow aspirate and the whole blood specimen are collected for the correlative study A041202-PP1, described in Section 10.3. From patients who consent to model consent question #2, collect 1 mL of bone marrow aspirate and 10 mL (2 x 5 mL tubes) of whole blood in an EDTA tube at baseline.

Specimens for patients registered on this study must be logged and shipped using the online Alliance BioMS, as described in Section 6.2.

The specimens should be labeled with the study number (A041202), Alliance patient ID, patient's initials, institution, and date and time of specimen procurement, and sample type. A copy of the shipping manifest produced by the BioMS must be printed and placed in the shipment with the specimens and sent to the Alliance Hematologic Malignancy Biorepository (HEME):

Alliance Hematologic Malignancy Biorepository
The Arthur G. James Cancer Hospital and Research Institute
300 West 10th Avenue, Lobby
Columbus, OH 43210
Tel: 614-688-4754 Fax: 614-688-4755

Ship specimens on a cold pack by overnight courier to the Alliance Hematologic Malignancy Biorepository (HEME) the same day they are collected. Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery" and "Priority Overnight Service". Do not ship specimens on Saturdays. Please be sure to use a method of shipping that is secure and traceable.

6.3 Geriatric Assessment (Alliance A041202-EL1)

Correlative study A041202-EL1 is described in Section 10.2. For patients who consent to model consent question #1, the following questionnaires are to be submitted via Medidata Rave:

Questionnaire/Survey	To be completed by	Submission Time Points (+/-30 days)		
		Prior to treatment*	Day 1 of Cycle 6	Progression or 2 Years
Self Geriatric Assessment Measure - Patient Questionnaire	Patient	X	X	X
Health Care Professional Questionnaire	Nurse, CRA or Physician	X	X	X

* Between pre-registration and start of cycle 1.

A member of the research team at each participating institution must complete a brief training on the geriatric assessment procedures (see Section 5.4.2).

Geriatric Assessment questionnaire booklets for A041202-EL1 are to be ordered prior to the registration of any patients. The healthcare professional questionnaire and patient completed questionnaire booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the CTSU A041202 Webpage) and faxing the form to the CTSU Data Center. Samples of questionnaires found in Appendix V of the protocol document are for reference and IRB submission only. They are not to be used for patient completion.

See Section 6.1 for data submission and Section 10.2 for instructions regarding the Alliance A041202-EL1 correlative science companion study.

7.0 REQUIRED DATA

Laboratory and clinical parameters during the treatment courses are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this protocol will be cared for by physicians experienced in the treatment and supportive care of patients with leukemia. Sections 11.0 & 16.0 describe possible toxicities that may occur with protocol treatment.

Pre-Study Testing Intervals

To be completed within 30 DAYS before registration:

- FISH for del(11q22.3) and del(17p13.1)
- Peripheral blood flow cytometry
- Bone marrow biopsy
- CT scans
- HBsAg, HBsAb, Hep C, HB core antibody
- Serum immunoglobulins
- Beta 2 microglobulin

To be completed within 14 DAYS before registration:

- All blood work (except FISH analysis, peripheral blood flow cytometry, central Zap-70 hepatitis antibodies, immunoglobulins, and beta 2 microglobulin)
- History and physical

Tests & Observations[1]	Prior To Study	Cycle 1 Day 1	Day 1 of Cycles 2, 3, 4, 5, 6	Day 1 of Every Third Cycle During Treatment, Arm 1 Observation & Clinical Follow-up*, **	Relapse/ Disease progression ***	Prior to Re-registration ****
History & progress notes [3]	X		X	X	X	X
Physical examination and node measurements[3]	X		X	X	X	X
Height [3]	X					X
Weight / body surface area [3, 4]	X		X	X		X
Performance status	X		X	X	X	X
Solicited baseline abnormalities/AEs	X		X	A		X
Registration fatigue/uniscale assessment	B					
Laboratory Studies[1]						
FISH for del(11q22.3) and del(17p13.1) (performed locally) [2, 3]	X					
Zap-70 methylation (central analysis) [3, 5]	X					
Complete blood count (CBC)	X	X	X	X	X	X
Serum creatinine, CrCl (est.), BUN	X	X	X	A		X
Serum electrolytes	X	X	X	A		X
Uric acid / glucose / phosphate / Ca^{++}	X					X
AST, ALT, PT INR, alk. phos., bilirubin	X		X	A		X
LDH, albumin	X		X	A		X
Beta-2-microglobulin	X					X
Direct antiglobulin test (Coomb's test)	X					X
Serum or urine HCG[9]	X					X
HBsAg, HBsAb, Hep C, HB core antibody [6]	X					X
Peripheral blood flow cytometry [3]	X		G	H	X	I
Serum immunoglobulins (IgG, IgA, IgM)	X		G	C		
Staging						

CT scan (chest, neck, abdomen, & pelvis) [1, 3]	X		G	H	X	I
Bone marrow asp. & biopsy [1, 3, 7]	D			F	F	I
Additional Required Correlative Samples[8]						
Peripheral whole blood	X		E	H	X	
Buccal cell sample	X					

* For patients in clinical follow up (see definition in Section 14.1.3), Cycle 9 and Cycle 27 visits may be performed +/- 1 follow-up cycle (i.e. Day 1 of Cycles 8 or 10, or Cycles 26 or 28).

** These studies are required for all patients in Arm 1 observation, those continuing to receive ibrutinib on Arms 2 and 3, and those in clinical follow-up. These studies are required every third cycle until progression or 10 years from study registration (step 1), (see Section 14.1.3 for complete definitions).

*** Required for all patients at time of progression/relapse. For patients who have already crossed over, these studies are also required for second progression/relapse.

****Patients on Arm 1 who progress and crossover to single agent ibrutinib should restart the study calendar after re-registration (i.e. the first day of ibrutinib would be considered Day 1 of Cycle 1). Crossover patients should follow the calendar as if they are assigned to Arm 2, unless stated otherwise in the following footnotes. See Section 6.2.1 for other specimen submission instructions.

1 Tests & observations and laboratory studies can be performed up to 48 hours prior to Day 1 of the specified cycle. CT scans and bone marrow biopsy may be completed up to 7 days prior to specified cycle.

2 FISH can be performed on peripheral blood (preferred) or bone marrow.

3 Reports and clinic notes must be submitted in PDF form via Medidata Rave. Bilateral measurements of largest nodes on CT are required.

4 The dose of chemotherapy need not be changed unless the calculated dose changes by ≥ 10%.

5 All patients will undergo Zap-70 methylation centrally prior to randomization. Within 10 days of receipt of the specimens, the treating physician/institutional contact will be notified of the results. See Section 6.2.1..

6 All patients should be screened for hepatitis B prior to registration. Patients who test positive for hepatitis B should be monitored closely if randomized to receive rituximab, and should be considered for prophylactic antiviral therapy.

7 Bone marrow analysis should include flow cytometry.

8 Included here are only the specimens to be submitted for the required correlative study A041202-LC1 (please see Sections 5.4, 6.2.1, and 10.1). Additional correlative specimens and data are to be collected from patients who consent to the optional correlative studies A041202-EL1 and A041202-PP1 (model consent questions # 1 and 2), as well as those who enrolled on CALGB 9665 prior to the temporary suspension on February 28, 2014. Please see Sections 5.4, 6.2.1, 6.3, 10.2 and 10.3, as well as the companion protocol for CALGB 9665 for further information on the additional optional correlative and companion studies.

9 Only required for women of childbearing potential.

A Ongoing solicited adverse event forms and indicated laboratory studies are only necessary for patients still on ibrutinib (Arms 2 and 3).

B To be completed after registration and ≤ 21 days prior to treatment, see Section 1.7 and Appendix III.

C Serum immunoglobulin should be on Day 1 of Cycle 9 for all patients. For patients on continuous ibrutinib (Arms 2 and 3), perform serum immunoglobulins on C9D1, C12D1. C27D1, and then, perform yearly.

D In addition to institutional marrow, submit specimens for central morphology review (see Section 6.2.2) and A041202-LC1 correlative (see Sections 6.2.1 and 6.2.4.1).

E Submit only on Day 1 of Cycle 2 for patients on continuous ibrutinib (Arms 2 and 3). See Section 6.2.1.

F For all patients, perform Day 1 of Cycle 9, Day 1 of Cycle 27, and at relapse or disease progression. In addition to institutional marrow, submit bone marrow aspirate for A041202-LC1 as required in Sections 6.2.1 and 6.2.4.1.

G Day 1 of Cycle 4 only (not required for Day 1 of Cycles 2, 3, 5 and 6).

H Perform Day 1 of Cycle 9 and Day 1 of Cycle 27 only.

I CT scan, peripheral blood flow cytometry, and bone marrow aspirate, biopsy and flow cytometry results can be used from progression visit and do not need to be repeated, nor do they need to fall within 14-day window prior to re-registration.

8.0 TREATMENT PLAN

Questions regarding treatment should be directed to the Alliance Study Chair. All patients will undergo FISH (institutionally) for del(17p13.1) and del(11q22.3) as well as Zap-70 methylation (centrally) prior to randomization. FISH and Zap-70 methylation results must be documented on enrollment form. After registration, the institutional contact will receive a registration confirmation and treatment registration that includes the randomization arm. Protocol treatment is to begin within 7 days of patient registration.

All patients should be screened for hepatitis B prior to registration. Patients with a positive hepatitis B core antibody but with negative hepatitis B DNA may participate, but must have hepatitis serologies and hepatitis B DNA monitored periodically by the treating physician.

It is acceptable for individual chemotherapy doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. New cycles of ibrutinib can be started up to 7 days before the protocol-defined date for major life events. Documentation to justify a delay or advance of a cycle should be provided.

8.1 Arm 1: Bendamustine/Rituximab

Treatment on Arm 1 consists of six 28-day cycles. The day **before** day 1 of cycle 1 (day 0), rituximab is given at 375 mg/m^2 IV, then at 500 mg/m^2 IV on day 1 of cycles 2-6. Bendamustine is given at 90 mg/m^2 IV on days 1 and 2 of each cycle. During cycle 1, at the discretion of the treating investigator, the bendamustine may be given at a dose of 70 mg/m^2 rather than 90. Subsequent cycles should be administered at 90 mg/m^2.

- **Recommended/prohibited ancillary therapy is outlined in Section 12.0**
- **Premedication:** Premedication per institutional guidelines is permitted, however, recommended premedication is the following:
  - **Bendamustine:** ondansetron 16 mg IV prior to each dose
  - **Rituximab:** acetaminophen 650 mg PO and diphenhydramine (or equivalent antihistamine) 50 mg PO/IV 30 minutes prior to each dose; other premedications may be given per institutional guidelines.
- **Drug administration**

  Full administration guidelines are outlined in Section 11.0 Bendamustine and rituximab are both administered intravenously. Bendamustine should be administered prior to rituximab on days that they are both given, but the order of administration may be altered per institutional guidelines.
- **Dose modifications/dose delays after cycle 1 are outlined in Section 9.0.**
- Patients enrolled on Arm 1 bendamustine plus rituximab will be eligible to cross over to single-agent ibrutinib upon documentation of disease progression. These patients will remain on ibrutinib until they experience a second disease progression. The follow-up schedule for those patients who remain on ibrutinib should match those of Arm 2.

8.2 Arm 2 Ibrutinib

Treatment on this arm consists of ibrutinib 420 mg PO daily, on days 1-28 of each 28-day cycle, until disease progression as defined by IWCLL guidelines.[28] Because of the well-documented

lymphocytosis that occurs early with this agent and is not associated with disease progression, progressive lymphocytosis in the absence of other signs of disease progression (e.g. splenomegaly, enlarging lymph nodes, disease-related constitutional symptoms) **will not** be considered disease progression.

- **Recommended/prohibited ancillary therapy is outlined in Section 12.0.**
- Premedication is not required.
- **Drug administration**

  Full administration guidelines are outlined in Section 11.0. Ibrutinib is administered by mouth as three capsules daily.
- Patients on ibrutinib should keep a daily drug administration record with dates and times taken (see Appendix I, Patient Medication Diary).
- If a dose of ibrutinib is missed, it can be taken as soon as possible on the same day with a return to normal schedule the following day. The patient should not take extra capsules to make up the missed dose, and any remaining study drug must be returned at the next scheduled visit.
- Dose modifications/dose delays after cycle 1 are outlined in Section 9.0.

8.3 Arm 3 Ibrutinib/Rituximab

Treatment on this arm consists of ibrutinib 420 mg PO daily, on days 1-28 of each 28-day cycle, plus rituximab 375 mg/m^2 IV weekly for four weeks starting on cycle 2 day 1 (days 1, 8, 15, and 22), then day 1 of cycles 3 through 6. Ibrutinib will be continued past cycle 6 until disease progression. Because of the well-documented lymphocytosis that occurs early with this agent and is not associated with disease progression, progressive lymphocytosis in the absence of other signs of disease progression (e.g. splenomegaly, enlarging lymph nodes, disease-related constitutional symptoms) **will not** be considered disease progression.

- **Recommended/prohibited ancillary therapy is outlined in Section 12.0.**
- **Premedication**

  No premedication is required for ibrutinib. Rituximab premedication per institutional guidelines is permitted. Recommended premedication is acetaminophen 650 mg PO and diphenhydramine 50 mg PO/IV (or equivalent antihistamine) 30 minutes prior to each dose
- **Drug administration**

  Full administration guidelines are outlined in Section 11.0. Ibrutinib is administered orally as three capsules daily, and rituximab is administered intravenously. Ibrutinib should be administered prior to rituximab on days when both agents are given.
- Patients on ibrutinib should keep a daily drug administration record with dates and times taken.
- If a dose of ibrutinib is missed, it can be taken as soon as possible on the same day with a return to normal schedule the following day. The patient should not take extra capsules to make up the missed dose, and any remaining study drug must be returned at the next scheduled visit.
- **Dose modifications/dose delays after cycle 1 are outlined in Section 9.0**.

9.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

9.1 Dose Modifications for Hematologic Toxicity

G-CSF and GM-CSF may not be used prophylactically to avoid dose reductions, but may be used in cases of prolonged or recurrent neutropenia or in a patient who has had neutropenia with previous cycles. Dose modifications should be made based on day 1 values for each cycle, or the presence of significant bleeding or febrile neutropenia. Hematologic toxicity will be graded according to IWCLL 2008 criteria[28], which account for pretreatment cytopenias. These are graded as follows:

Grade	Decrease in Platelets* or Hgb** from pretreatment value	Absolute Neutrophil Count (ANC) (uL)***
1	11%-24%	≥1500 and <2000
2	25%-49%	≥1000 and <1500
3	50%-75%	≥500 and <1000
4	≥75%	<500

*Platelet counts must be below normal levels for any grade toxicity to be recorded. If platelet count is $<20x10^{12}$/L, this will be considered grade 4 toxicity.
**Hgb levels must be below normal levels for any grade toxicity to be recorded.
***If ANC is <1000 prior to study, the patient is not evaluable for toxicity assessment based on ANC.

9.1.1 Arm 1

Dose Level	Bendamustine	Rituximab
1 (starting dose)	90 mg/m^2	500 mg/m^2
-1	50 mg/m^2	500 mg/m^2
-2	30 mg/m^2	500 mg/m^2

- For grade 3 or 4 hematologic toxicity (or significant bleeding), hold therapy until toxicity returns to ≤ grade 1, and then dose reduce by 1 level. If patient experiences grade 3 or 4 toxicity at dose level -2, protocol therapy should be discontinued.
- For febrile neutropenia, hold therapy until fever resolves and ANC is >1000, and then dose reduce by 1 level. If patient experiences febrile neutropenia at dose level -2, protocol therapy should be discontinued.
- Once reduced, dose levels may not be escalated

9.1.2 Arm 2

Dose Level	Ibrutinib
1 (starting dose)	420 mg
-1	280 mg
-2	140 mg

- For grade 3 or 4 hematologic toxicity, significant bleeding, or febrile neutropenia, hold therapy until toxicity returns to ≤ grade 1. For the first occurrence, drug may be restarted at the original dose. For the second occurrence and beyond, dose reduce by 1 level.
- Ibrutinib may be held for up to 28 consecutive days for drug-related toxicity. If drug-related toxicity persists, ibrutinib must be discontinued permanently.
- Patients who are dose-reduced and are stable for 3 months may have dose escalated 1 level.

- Upon initiation of treatment, a transient phase of increase in lymphocyte counts (i.e., ≥50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. A substantial increase in the number of circulating lymphocytes (e.g., > 400,000/mcL) has been observed in a subset of patients. There have been isolated cases of leukostasis reported in patients treated with ibrutinib.

  A high number of circulating malignant cells (>400000/mcL) may confer increased risk; these patients should be closely monitored. Administer supportive care such as hydration and/or leukapheresis as indicated. Ibrutinib should be held if evidence of leukostasis until resolution of toxicity.

9.1.3 Arm 3

First 6 months

Dose Level	Ibrutinib	Rituximab
1 (starting dose)	420 mg	375 mg/m2
-1	420 mg	No rituximab
-2	280 mg	No rituximab
-3	140 mg	No rituximab

Subsequent months

Dose Level	Ibrutinib
1 (starting dose)	420 mg
-1	280 mg
-2	140 mg

- For grade 3 or 4 hematologic toxicity, significant bleeding, or febrile neutropenia, hold therapy until toxicity returns to ≤ grade 1. For the first occurrence, drug may be restarted at the original dose. For the second occurrence and beyond, dose reduce by 1 level.
- Ibrutinib may be held for up to 28 consecutive days for drug-related toxicity. If drug-related toxicity persists, ibrutinib must be discontinued permanently.
- Patients who are dose-reduced and are stable for 3 months may have dose escalated 1 level.
- Upon initiation of treatment, a transient phase of increase in lymphocyte counts (i.e., ≥50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. A substantial increase in the number of circulating lymphocytes (e.g., > 400,000/mcL) has been observed in a subset of patients. There have been isolated cases of leukostasis reported in patients treated with ibrutinib.

  A high number of circulating malignant cells (>400000/mcL) may confer increased risk; these patients should be closely monitored. Administer supportive care such as hydration and/or leukapheresis as indicated. Ibrutinib should be held if evidence of leukostasis until resolution of toxicity.

9.2 Dose Adjustments for Non-Hematologic Toxicity

Dose Level	Bendamustine	Ibrutinib
1 (starting dose)	**90 mg/m^2**	**420 mg**
-1	**50 mg/m^2**	**280 mg**
-2	**30 mg/m^2**	**140 mg**

- For grade 3 or 4 non-hematologic toxicity at possibly, probably, or definitely related to bendamustine, hold bendamustine and rituximab until toxicity returns to ≤ grade 1, and then dose reduce by 1 level. If patient experiences grade 3 or 4 toxicity at dose level -2, bendamustine should be discontinued, but rituximab can continue for total course or can be discontinued at the discretion of the treating physician.
- For grade 3 or 4 non-hematologic toxicity at least possibly, probably, or definitely attributable to ibrutinib, hold ibrutinib until toxicity returns to ≤ grade 1. For a first occurrence, ibrutinib may then be restarted at the same dose. For a second occurrence, once toxicity resolves, dose reduce by 1 dose level. Prior to dose reduction for diarrhea, aggressive supportive care should be instituted. Recommended agents for ibrutinib-induced diarrhea include cholestyramine and diphenoxylate/atropine.
- For infusion reactions attributable to rituximab, supportive care should be provided per institutional protocols. Rituximab can be continued without dose reduction. At the discretion of the treating physician and with study chair approval, rituximab and/or bendamustine can be discontinued for severe infusion reactions.
- Rituximab should be discontinued in the following circumstances: progressive multifocal leukoencephalopathy (PML), significant vesicular or bullous dermatitis, Stevens-Johnsons syndrome, or development of hepatitis B reactivation.
- Patients who require the initiation of systemic anticoagulation should have ibrutinib held and be placed on low molecular weight heparin (concomitant warfarin therapy is prohibited). 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.
- For Grade 3 or 4 skin reactions or infusion reaction/anaphylaxis at least possibly, probably or definitely attributable to bendamustine, bendamustine should be permanently discontinued and rituximab may be discontinued as well at the discretion of the treating physician.
- 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.
- Ibrutinib is metabolized in the liver. Please see the Child-Pugh scoring system outlined in Appendix VI 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 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.

- 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 as outlined in Section 16.1.
- For Grade 2 toxicity that is causing significant discomfort or functional impairment, dose interruption and modifications may be made using the same guidelines as for Grades 3 and 4 at the discretion of the treating physician and after discussion with the study chair.

9.3 Dose Modifications for Obese Patients

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 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 calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation

10.0 EMBEDDED CORRELATIVE SCIENCE COMPANION STUDIES

There are three embedded correlative science companion studies. Patients are required to participate in A041202-LC1, and encouraged to participate in A041202-EL1 and A041202-PP1.

10.1 Leukemia Correlative Science in Alliance 041202 (Alliance A041202-LC1)

10.1.1 Background

Previous CLL research identified specific markers including cytogenetic abnormalities, Zap-70 methylation, and IgVH mutational status that predict both the natural history of this disease and response with specific therapies. With the studies performed in relapsed disease, it appears that the traditional genetic markers that predict poor response, including del(17p13.1), del(11q22.3) and complex karyotype are unrelated to outcome with ibrutinib. In patients with del(17p13.1), ORR in relapsed disease is 67%.[21] Further, the traditionally poor markers of IgV_H unmutated disease and lack of Zap-70 methylation, which are associated with active BCR signaling are associated with improved responses to ibrutinib. We hypothesize that CLL cells with active BCR signaling pathways are dependent on this pathway for survival, and thus are more sensitive to BTK inhibition. These data require confirmation in a larger data set, but suggest that novel markers in this disease may be important to response and response duration with ibrutinib. Gene and miR expression profiling at baseline will be studied for signatures of extended PFS to treatment arms proposed. Recently, whole genome sequencing has identified recurrent DNA mutations in CLL in SF3B1, NOTCH1, CRM1, MyD88, KLHL6, ERK1, and B-RAF with potential correlates to disease behavior and response to therapy.[29-31] NOTCH1 mutations are the most common in this series, with an overall prevalence of 12.2%, with 20.4% prevalence in unmutated CLL, and a relationship with poorer overall survival. Additionally, mutational frequency is higher in those patients with refractory disease or Richter's transformation.[32] SF3B1 mutations as well have been identified in up to 15% of patients with CLL,[31] with initial studies suggesting an association between mutations in this RNA splicing factor and poor-risk or fludarabine-refractory disease.[30, 33]

All specimens included in these baseline correlative studies will be shipped to Ohio State University. For stimulated cytogenetics, samples will be stimulated using CpG oligonucleotides, and at least 20 metaphases will be examined for each patient. For FISH analysis, the following probes will be used: 17p13.1(TP53), 13q14.3(DS13S319),

11q22.3(ATM), 6q21(SEC63), 3q27(BCL6), 8q24(CMYC), 14q32.3-11q13(IgH-CCND1), and centromere 12. FISH will be performed per manufacturer's guidelines, and at least 200 cells will be analyzed for each probe. To determine whether local FISH analysis is feasible for future studies, for this trial FISH analysis for del(11q22.3) and del(17p13.1) will be performed locally and centrally at baseline and results compared for each patient. Dr. Nyla Heerema at Ohio State University will perform FISH and cytogenetic studies.

Zap-70 methylation will be performed by pyrosequencing at Ohio State University. If, by the time this protocol is in place, a clinical Zap-70 test is not available, Zap-70 will be performed on a research basis and IgVH will be used for patient stratification. In the event that a sample does not yield a result after re-analysis, data will be input based on IgVH mutational status as follows: >20 if IgVH mutated or <20 for unmutated.

DNA mutational analysis will be performed at Ohio State University in the laboratory of Dr. John Byrd using ion semiconductor technology (Ion Torrent). Baseline samples will be saved for future comparison with relapse samples.

Samples will also be collected at 1 month for patients on ibrutinib, 9 months and at the time of relapse. Samples obtained at 1 and 9 months will be paired with baseline samples and used to examine changes in gene or microRNA expression in cells or plasma microvesicles. These analyses will be performed using Nanostring technology, and will be run at Ohio State University. Specifically, these samples will allow for validation of miRs and genes changing with ibrutinib, comparisons among subsets of patients with persistent lymphocytosis, and those who relapse later in therapy. These studies will hopefully identify groups of patients most likely to benefit from ibrutinib and also mechanisms of primary and secondary resistance. These samples will be saved in the Alliance Hematologic Malignancy Biorepository for future use.

The eradication of MRD following chemotherapy and CIT is an independent predictor of PFS and OS;[10, 34] however, MRD has not been evaluated in the context of targeted therapies. This phase III trial has the potential to definitively determine whether MRD negativity is required for durable response with kinase inhibitors in CLL. MRD will be determined by high sensitivity 4 color flow cytometric analysis of the bone marrow using validated panels. A sample will be classified as positive if 50 or more lymphocytes (out of 500,000 total leukocyte events) are positive for CD5, CD19, CD43, and CD45 bright, and negative for CD10, CD79b, and CD81. Dr. Gerard Lozanski at Ohio State University will perform these studies.

10.1.2 Objectives

- To determine whether baseline cytogenetic markers, Zap-70 methylation, IgVH mutational status, or select DNA mutations predict outcomes or time to response in these three arms
- To determine whether local FISH results for del(11q22.3) and del(17p13.1) are consistent with central analysis
- To determine whether baseline microRNA and gene expression markers in cells or plasma microvesicles are correlated with clinical outcomes of interest (e.g. progression-free and alive at 2 years versus not) as well as to explore changes in microRNA expression from baseline to post-treatment time points, with a focus on those with persistent lymphocytosis and relapse
- To determine whether eradication of MRD predicts longer duration of response with standard therapy and ibrutinib-based regimens

10.1.3 Sample Requirements

Baseline

Peripheral Blood: 4x10 mL acid citrate dextrose (ACD) tubes, 1x 5 mL heparin tube, 1 x 5 mL EDTA tube

Bone marrow: 1 x 10 mL EDTA tube

Buccal cell sample: 50 mL sterile tube

Day 1 Cycle 2 (patients on Arm B and C only)

Peripheral Blood: 4x10 mL acid citrate dextrose (ACD) tubes

Day 1 Cycle 9

Peripheral Blood: 4x10 mL acid citrate dextrose (ACD) tubes

Bone marrow: 1x10mL EDTA tube

24 months

Peripheral Blood: 4x10 mL acid citrate dextrose (ACD) tubes

Bone marrow: 1x10 mL EDTA tube

Time of Relapse/Progression

Peripheral blood: 4x10 mL acid citrate dextrose (ACD) tubes, 1x10 mL heparin tube

Bone marrow: 1 x 10 mL EDTA tube

10.2 Geriatric Assessment in Alliance A041202 (Alliance A041202-EL1)

10.2.1 Background

It is widely accepted that chronologic age is not the optimal indicator on which to estimate functional status and ability to tolerate specific therapies or procedures. The older patient population seen in CLL makes it especially important to evaluate patients based on criteria other than chronologic age. A measurement tool has been developed by the Alliance Cancer in the Elderly Committee which evaluates patients based on functional status has been shown to be feasible in the cooperative group setting.[35] This tool has been used both to describe the functional status of cohorts of patients and to predict chemotherapy-associated toxicity.[36] The assessment incorporates measures in six domains; Functional status, comorbidity, psychological state, social activity, social support, and nutrition.[37] The following tools are included in the assessment: Activities of Daily Living, Instrumental Activities of Daily Living, Karnofsky Performance Status, Number of Falls in 6 months, timed 10-foot walk, comorbidity assessment from Older American Resources and Services Evaluation, Blessed Orientation-Memory-Concentration Test, Hospital Anxiety and Depression Scale, Medical Outcomes Study Social Activity and Social Support Surveys, Body Mass Index, and weight loss over 6 months. This evaluation will be used in the context of this study to describe the global functional status of the patients at baseline, evaluate prediction of chemotherapy-associated toxicities with targeted agents, and evaluate patients longitudinally with therapy. Longitudinal assessment will allow further exploration of tolerability of these agents, as well as changes in functional status that correlate with disease control and long-term toxicity. This assessment will be optional for all patients, but institutions must offer the correlative study to all patients enrolling on the treatment study.

10.2.2 Study Design

The intent is to enroll 350 patients onto this substudy. To obtain the 350 patients, consecutive patients enrolled on the parent study will be asked to participate on this study until 350 patients are obtained or until accrual to the parent study has stopped, whichever

happens first. Patients will complete the geriatric functional assessment at baseline (between pre-registration and cycle 1 day 1), day 1 of cycle 6, and at the end of study (progression, study discontinuation for toxicity or patient choice) or at 2 years. Median time to complete the assessment is 15 minutes for patients, and 5 minutes for research staff, who are required for the Karnofsky performance status assessment, a timed 10 foot walk, and the 6 question Blessed Orientation-Memory-Concentration Test.[35]

Geriatric Assessment questionnaire booklets for A041202-EL1 are to be ordered prior to the registration of any patients. For booklet ordering instructions see Section 6.3.

10.2.3 Objectives

The Geriatric Functional Assessment will be used in the context of this trial to address the following questions:

10.2.3.1 To describe the baseline functional status, comorbid medical conditions, and number of medications of older CLL patients who meet criteria for therapy

Hypothesis: Older patients with CLL who meet criteria for therapy will need assistance with instrumental activities of daily living, have multiple comorbid medical conditions, and be on medications for conditions besides leukemia.

Rationale: As many CLL studies include predominantly younger patients, and functional status measurements are not routinely incorporated into CLL trials, there is little information about the functional status of the typical older CLL patient who requires therapy for disease. While these patients will likely still overestimate the true functional status of the CLL population (because of self-selection for clinical trial participation, ability to travel to a tertiary center in some cases, and ECOG PS that allows study entry), it will provide valuable information regarding this patient population.

Statistical Considerations: The anticipated sample size for this aim is 350 patients. This will be a descriptive analysis. Summary statistics and corresponding 95% confidence intervals will be generated for baseline functional status, comorbid medical conditions, and the number of medications a patient is taking.

10.2.3.2 To determine how functional status changes with therapy using baseline to 6 month evaluation and end of study / 2-year evaluation. To determine whether this change is different among the treatment groups

Hypothesis: Functional status will significantly improve with therapy. The magnitude of change will be greater with ibrutinib-containing regimens.

Rationale: With disease control, it is very likely that functional status will improve. However, functional status can also be limited because of treatment-associated toxicity or the rigor of being on therapy (multiple doctor visits with blood draws, radiology, infusions), so it is important to balance therapy efficacy and tolerability. Ibrutinib has been very well tolerated, so it will be interesting to investigate whether this tolerability translates into improved functional status for this group.

Statistical Considerations: It is assumed that 90% of the initial 350 patients will be assessed for functional status at 6 months and 60% will be assessed at 2 years; this corresponds to a 20% attrition rate we observed on other studies. With 315 patients assessed at 6 months (i.e. 90% of 350), a 0.367 standard deviation difference in

standardized means can be detected between patients treated with bendamustine+rituximab and patients treated with ibrutinib +rituximab with power of 90% and a two-sided alpha level of 0.05. In general, a 0.5 standard deviation change in functional status score is considered clinically meaningful and so this aim has sufficient power to detect a clinically meaningful difference between the arms. This is a simplistic calculation and the more sophisticated analysis described below will likely have more power because it will analyze the changes across all timepoints.

Analysis of covariance with repeated measures will be used to analyze the functional status changes between the two treatment arms if the attrition over time is relatively minimal. Treatment arm will be the independent variable (bendamustine+rituximab versus ibrutinib+rituximab) and the functional status score will be the dependent variable. Baseline comorbid conditions and socio-demographic factors will be entered as covariables. If attrition is considerable over the course of the substudy, a pattern mixture model will be used to analyze change in functional status over time by treatment arm, for each subset of patients maintained on the study for different lengths of time. [38, 39]Within the structure of the pattern mixture model, a random coefficient model will be used to control for other mediating factors including socio-demographic factors and baseline co-morbid conditions. Clinical significance of the findings will be further tested using logistic regression analysis to determine whether treatment arm is significantly predictive of those patients with a meaningful functional decline, defined as a drop of 0.50 standard deviations or greater in their baseline functional status score, at 6 months and 2 years.

Although ANOVA with repeated measures will be the primary analysis if the amount of missing data < 20%, sensitivity analyses, including the use of pattern mixture modeling, will be conducted to determine the effect of "missingness" on the inferences. If the results are different using these two methods, the pattern mixture modeling approach will be used.

10.2.3.3 To determine whether geriatric assessment variables known to be associated with chemotherapy toxicity in other disease groups can also predict therapy-associated toxicity in the CLL population

Hypothesis: A predictive model for chemotherapy adverse events (AEs) will be able to predict therapy-associated AEs in this patient population.

Rationale: Baseline variables identified in a predictive model for chemotherapy AEs[36] can also predict significant AEs (defined as grade 3+ AEs) associated with ibrutinib containing-regimens and confirm that specific geriatric assessment tools can predict AEs associated with cancer therapy in elderly patients.

Statistical Considerations: We will assess incidence of serious (grade 3 or higher) adverse events in each of the treatment arms; based on previous data, we expect a 50% grade 3+ AE rate with standard therapy, a 25% grade 3+ AE rate in the ibrutinib alone arm, and a 30% rate in the ibrutinib + rituximab arm. Toxicity associated with bendamustine+rituximab is expected to be primarily hematologic.[10] AEs associated with ibrutinib or ibrutinib + rituximab is expected to be hematologic as well as diarrhea, rash, and fever.[21, 22]

The expected sample size for this aim is 350 patients. The primary analysis will be to use the various geriatric scores that were found to be predictive of serious adverse events in other patient populations (an AE of grade 3 or higher). This will be assessed

by determining whether the area under the curve (AUC) of a receiver operating curve (ROC) is statistically, significantly greater than 0.50, the value that is no better than chance. The analyses will be done for each arm separately, which will involve approximately 157 patients. There is approximately 90% power to detect an AUC of 0.60 or greater, regardless of what the split is between patients with a serious AE and patients without a serious AE with a sample size of 157. AUCs that would be of interest are between 0.70 and 0.90. Hence, this study will have greater than 99% power to detect differences of this magnitude. This is an exploratory (NOT confirmatory analysis) and further studies will be warranted if we observe AUC values above 0.70.

Models using baseline assessments will be used to predict who will experience a grade 3 or higher adverse event. We will examine the associations between an occurrence of a grade 3+ (i.e. grade 3, 4, or 5) adverse event and the baseline geriatric assessment variables using logistic regression. These analyses will be done separately for each treatment arm as well as jointly using models that include treatment arm and a treatment/geriatric assessment interaction term. A comparison of those variables found to be statistically significantly associated with a grade 3+ AE for this patient population will be compared to those found to be associated in other patient populations. A level of significance of 0.05 will be used (no adjustment for multiple comparisons since we are determining whether associations found significant in other disease groups are also significant here).

In addition, we will test any prognostic model that has been developed for other disease groups that use the geriatric assessment variables. To do this, we will develop a multivariable logistic regression model for predicting a grade 3+ AE using the variable in the prognostic model for other disease groups. We will then perform a receiver operating characteristic (ROC) analysis and determine whether the area under the curve (AUC) differs significantly from 0.5, which would indicate the model has predictive power.

If existing models do not validate, we will develop a new prognostic model for AEs from the baseline assessments. All factors with univariable p-value less than 0.2 will be considered, including the potential for interactions of interest. The performance of the new model will be compared to existing models to determine whether it potentially has greater discriminatory ability by comparing the AUCs of each model.

10.3 Evaluation of Candidate Pharmacogenetic Determinants of Ibrutinib or Ibrutinib/Rituximab Response (Alliance A041202-PP1)

10.3.1 Background and Hypothesis

Pharmacogenetic studies will focus on the hypothesized synergistic interaction of ibrutinib and rituximab. The tendency of ibrutinib to cause a peripheral lymphocytosis (perhaps due to disruption of bone marrow/lymph node homing mechanisms) combined with the rapid clearance of peripheral B-cells observed after rituximab treatment is the proposed basis of this synergy. Several germline polymorphisms can predict rituximab sensitivity. A polymorphism in *FCGR3A*, encoding the Fc-gamma receptor on natural killer (NK) cells, has been shown to affect rituximab response in follicular lymphoma and DLBCL, but not in CLL[40-43]. We hypothesize that the effects of this polymorphism on antibody-dependent cell mediated cytotoxicity (ADCC), i.e. NK-cell mediated destruction of rituximab coated cells, will be more pronounced in CLL with the addition of ibrutinib. The three arms of this study provide controls to appropriately test this, since one arm has both agents, one has ibrutinib alone, and one has rituximab plus a cytotoxic agent (bendamustine). Therefore

effects specific to the proposed synergistic interaction between ibrutinib and rituximab can be assessed. Minimal residual disease (MRD) will be the primary endpoint.

In addition to the primary hypothesis, other hypotheses to be tested include a *C1QA* SNP (rs172378), shown to predict rituximab response in FL, but never tested in CLL[44, 45] *C1QA* encodes a complement protein, and presumably affects complement dependent cytotoxicity (CDC), another mechanism by which rituximab kills B-cells. These studies will also include the investigation of the candidate gene variation as well as novel high density single-nucleotide polymorphisms (SNP) platforms available to survey the pattern of variation of the entire genome of an individual, allowing the identification of genes that have not previously related to the pharmacology of the drugs of interest or to a certain biological pathway. Currently, platforms with hundreds of thousands of SNPs have been extensively used in so called genome-wide associations studies (GWAS) and do not only provide information of the SNP pattern of an individual, but also on the quantitative pattern on copy number variation (including loss of heterozygosity, LOH).

10.3.2 Objectives

The primary objective is to assess whether the *FCGR3A* polymorphism (rs396991) is correlated with depth of response (MRD status) to ibrutinib plus rituximab after 8 cycles.

The secondary objectives are to assess whether *CIQA* polymorphism (rs172378) is correlated with MRD status, CR rate, rapidity of response, and PFS. Thus, secondary endpoints will be CR rate, rapidity of response, and progression-free survival (PFS).

10.3.3 Methods

From the initial bone marrow aspirate, 0.5 mL will be used to culture fibroblasts to obtain germline DNA. If any patient who consents to PP1 is not able to have fibroblasts successfully cultured, a remaining portion of the LC1 buccal cell DNA sample may be used for this purpose. As a source of DNA for secondary correlative studies described below, whole blood will be obtained from consenting study participants at baseline, prior to receipt of study treatment. The blood will be sent to the Alliance Hematologic Malignancy Biorepository (HEME) for processing. Blood samples will be processed into plasma, PBL and DNA. If needed, B-cells can be removed by magnetic bead purification to eliminate CLL cells from the samples. DNA quality will be assessed by UV spectrophotometry and by agarose gel electrophoresis. All DNA samples will be stored at HEME until they are distributed to the appropriate laboratory for genotyping. For *FCGR3A* and *C1QA* SNPs, samples will be genotyped using previously established assays (Sequenom and Taqman, respectively). Phenotypic data will be extracted from the Alliance database by the Alliance Statistical Center. Center and statistical analyses will be conducted under the direction of the responsible Alliance primary statistician.

11.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

It is not necessary to change the doses due to changes in weight unless the calculated dose changes by ≥10%.

11.1 Rituximab (IDEC-C2B8)

Please refer to the FDA-approved package insert for rituximab for product information and a complete list of adverse events.

AVAILABILITY

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

STORAGE & STABILITY

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

PREPARATION

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

ADMINISTRATION

Rituximab will be administered by IV infusion. Patients must be pretreated with acetaminophen and diphenhydramine (or equivalent antihistamine) on each day of antibody treatment. On days on which both ibrutinib and rituximab are given, ibrutinib will be taken first, followed by rituximab administration.

Do not administer rituximab IV push or bolus. For the initial infusion, start at a rate of 50 mg/hour; if there is no reaction, increase the rate by 50 mg/hour increments every 30 minutes, to a maximum rate of 400 mg/hour. For subsequent infusions, if the patient tolerated the initial infusion, start at a rate of 100 mg/hour; if there is no reaction, increase the rate by 100 mg/hour increments every 30 minutes, to a rate of 400 mg/hour. If the patient did not tolerate the initial infusion, follow the initial infusion guidelines. If a reaction occurs, slow or stop the infusion. If the reaction abates, restart infusion at 50% of the previous rate. These guidelines are recommended. Individual institutions may follow institutional guidelines for rituximab administration.

TOXICITY

The most serious adverse events associated with rituximab include severe infusion reactions, tumor lysis syndrome, and severe mucocutaneous reactions. Severe infusion reactions consisting of hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock may be fatal. Most reported fatal reactions occurred within 24 hours of the first dose of rituximab. Because severe infusion reactions have been noted more frequently in patients with high leukocyte counts, such patients should be observed closely.

Tumor lysis syndrome resulting in renal failure has been described, and occasional fatalities noted. Tumor lysis syndrome is more likely in patients with high numbers of circulating malignant cells.

Severe mucocutaneous reactions associated with rituximab include Stevens-Johnson syndrome and toxic epidermal necrolysis. The onset of these reactions has been from 1-3 weeks.

Less severe infusion reactions are common with rituximab. These include fever, chills, and dyspnea. The mechanism of rituximab infusion reactions is thought to be the release of cytokines. If a reaction occurs, the infusion should be stopped until the symptoms resolve, and

then restarted at a 50% slower rate. Consider additional pre-medication with acetaminophen 650 mg PO and diphenhydramine 50 mg PO/IV (or equivalent antihistamine).

Recent reports describe hepatitis B reactivation with fulminant hepatitis, hepatic failure and death in some patients with hematologic malignancies treated with rituximab. The majority of these patients received rituximab in combination with chemotherapy. The median time to diagnosis of hepatitis was approximately 4 months after starting rituximab and approximately 1 month after the last dose.

Exacerbation or reactivation of other viral infections has also been reported with rituximab. Recent reports describe JC virus reactivation leading to progressive multifocal leukoencephalopathy (PML) in patients who were receiving rituximab. Patients presenting with new neurologic findings (e.g., major changes in vision, unusual eye movements, loss of balance or coordination, confusion) should be evaluated for PML.

A report in the literature described an increase in fatal infection in HIV-related lymphoma patients when rituximab was used in combination with CHOP chemotherapy, as compared to CHOP alone.

11.2 Ibrutinib (PCI-32765, NSC # 748645, IND #117241)

AVAILABILITY

Ibrutinib is supplied by Pharmacyclics, Inc., and distributed by the CTEP, DCTD, NCI. Ibrutinib is supplied as hard gelatin capsules containing 140mg micronized ibrutinib and the following excipients: microcrystalline cellulose; croscarmellose sodium; sodium lauryl sulfate; may contain magnesium stearate. Capsules are packaged in high-density polyethylene (HDPE) bottles with an induction seal and a child resistant screw top cap. Each bottle contains 92 capsules.

AGENT ORDERING AND AGENT ACCOUNTABILITY

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, 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 participating investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, and a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

STORAGE AND STABILITY

Ibrutinib hard gelatin capsules should be stored at 15-25°C (59-77°F). Shelf life surveillance of the intact bottles is ongoing.

ADMINISTRATION

Ibrutinib is taken orally, with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact, not less than 30 minutes before or 2 hours after a meal. Doses should be taken at about the same time each day. If the patient misses a dose, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra capsules to make up the missed dose.

TOXICITY

For a comprehensive adverse events and potential risks list (CAEPR), please see Section 16.2.

DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4/5. Please see Appendix II for a list of strong inhibitors and inducers.

Agents That May Increase ibrutinib Plasma Concentrations (CYP3A4/5 Inhibitors)

Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A4/5 can increase ibrutinib exposure and should be avoided. 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 (Cmax and AUC0-last) of ibrutinib by 29- and 24-fold, respectively. Therefore, concomitant administration of ibrutinib with strong inhibitors of CYP3A4/5 (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) 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. The same dose of ibrutinib

administered prior to the temporary hold or dose reduction may be given upon reinitiation of ibrutinib after CYP3A4/5 use. Moderate CYP3A4/5 inhibitors (aprepitant, erythromycin, fluconazole, verapamil, and diltiazem) 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. Grapefruit juices and Seville oranges may also increase ibrutinib plasma concentrations and should be avoided for the duration of ibrutinib treatment.

Agents That May Decrease ibrutinib Plasma Concentrations (CYP3A4/5 Inducers)

Administration of ibrutinib with strong inducers of CYP3A4/5 can decrease ibrutinib plasma concentrations. Physiologically based PK modeling and simulation indicates that rifampin, a strong inducer, can cause a 10-fold decrease in ibrutinib exposure. Strong CYP3A4/5 inducers (eg, carbamazepine, rifampin, phenytoin and St. John's Wort) can decrease ibrutinib exposure and therefore should be avoided. Alternative agents with less CYP3A4/5 induction should be considered.

QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic monitoring with ECGs and electrolytes should be considered and if needed, a medical monitor may be contacted.

Anticoagulation Therapy

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in patients requiring other anticoagulants or medications that inhibit platelet function. Patients with congenital bleeding diathesis have not been studied.

11.3 Bendamustine

Please refer to the FDA-approved package insert for bendamustine for product information and a complete list of adverse events.

AVAILABILITY

Bendamustine is supplied as a single-use vial containing 100 mg bendamustine HCL as white to off-white lyophilized powder

STORAGE & STABILITY

Bendamustine may be stored up to 25° C (77°F) with excursions permitted up to 30°C (86°F). Retain in original package until time of use to protect from light.

ADMINISTRATION

Bendamustine is administered by intravenous route over 30 minutes in 500 mL normal saline (to achieve a final concentration of 0.2-0.6 mg/mL).

TOXICITY

The most common side effect is bone marrow suppression. The most common non-hematologic adverse events in CLL (>15%) include pyrexia, nausea, and vomiting. Other adverse reactions seen frequently include asthenia, fatigue, malaise/weakness, dry mouth, somnolence, cough, constipation, headache, mucosal inflammation, and stomatitis.

Drug Interactions

Concomitant CYP1A2 inducers or inhibitors have the potential to affect the exposure of bendamustine.

12.0 ANCILLARY THERAPY

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. All blood products should be irradiated and leukopore filtered to prevent transfusion-associated graft versus host disease.

No prophylaxis is required for the administration of ibrutinib but may be administered if consistent with institutional guidelines. Institutional guidelines regarding supportive care related to bendamustine and rituximab infusions should be utilized. A suggested regimen is provided below:

Bendamustine: ondansetron 16 mg IV prior to each dose

Rituximab: acetaminophen 650 mg PO and diphenhydramine 50 mg PO/IV (or equivalent antihistamine) 30 minutes prior to each dose

Lymphocytosis

Upon initiation of treatment, a transient phase of increase in lymphocyte counts (i.e., ≥50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. A substantial increase in the number of circulating lymphocytes (e.g., > 400,000/mcL) has been observed in a subset of patients. There have been isolated cases of leukostasis reported in patients treated with ibrutinib.

A high number of circulating malignant cells (>400000/mcL) may confer increased risk. These patients should be closely monitored. Administer supportive care such as hydration and/or leukapheresis as indicated. Ibrutinib should be held if evidence of leukostasis until resolution of toxicity.

12.1 Alliance Policy Concerning the Use of Growth Factors

12.1.2 Epoetin Alfa / Darbepoietin Alfa

Use of epoetin alfa / darbepoietin alfa in this protocol is prohibited.

12.1.2 Filgrastim (G-CSF), pegfilgrastim, and sargramostim (GM-CSF)

1. Filgrastim (G-CSF), pegfilgrastim and sargramostim (GM-CSF) treatment is allowed per ASCO guidelines but not encouraged.
2. Filgrastim/pegfilgrastim and sargramostim:
   a. may not be used prophylactically to avoid dose reductions or delays
   b. may not be used prophylactically because of concern about myelosuppression from prior chemotherapies
3. For the treatment of febrile neutropenia the use of colony-stimulating factors (CSFs) should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting.
4. If filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

12.2 CYP Inhibiting Drugs

1. Concomitant use of strong CYP3A4/5 inducers or inhibitors is prohibited. Patients on these inhibitors should not be entered onto the study.

2. If use of a strong CYP3A4/5 inducer or inhibitor is indicated during the conduct of the study, selection of an alternate concomitant medication with less potent enzyme inhibition potential is strongly recommended. If a strong inducer or inhibitor is necessary, contact the study chair. If a strong inhibitor is needed, ibrutinib will be temporarily held or dose-reduced to 140 mg daily. Patients should be closely monitored for potential treatment-related toxicities.
3. Moderate CYP3A4/5 inhibitors (such as aprepitant, erythromycin, fluconazole, verapamil, and diltiazem) should be used with caution. 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.
4. Grapefruit juice and Seville oranges may also increase ibrutinib plasma concentrations and should be avoided for the duration of ibrutinib treatment.
5. A list of strong CYP3A4/5 inducers and inhibitors is found in Appendix II.

12.3 Surgery

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any surgery or invasive procedure requiring sutures or staples for closure, Ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For minor procedures (such as a central line placement, needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- 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.

12.4 Permitted Concomitant Medications

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

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

The 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.

12.5 Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp) 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.

13.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

Criteria for response will utilize the Revised IWCLL 2008[28] for response which includes clinical, hematologic, and bone marrow features as derived from the initial 1996 guidelines[46].

13.1 Response Criteria

13.1.1 Complete response: Requires all of the following for a period of at least two months:

- Absence of lymphadenopathy > 1.5 cm on physical exam and CT scan;
- No hepatomegaly or splenomegaly <u>on physical exam</u> **(a CT scan also may be used to assess)**;
- No clonal B-cells in the blood by flow cytometry;
- Normal CBC as exhibited by polymorphonuclear leukocytes ≥ 1,500/μL, platelets > 100,000/μL, hemoglobin > 11.0 g/dL (untransfused); lymphocyte count < 5,000/μL;
- Bone marrow aspirate and biopsy must be normocellular for age with < 30% of nucleated cells being lymphocytes. Lymphoid nodules may be present but must be T-cell in origin. If these are demonstrated to be clonal B-cells, patients should be considered to be a partial response. Additionally, if bone marrow is positive by two color flow cytometry for CLL cells, it should be considered a partial response. If the marrow is hypocellular a bone marrow should be performed in 2-3 months. If blood counts (polymorphonuclear leukocytes < 1,500/μL, platelets < 100,000/μL) fail to recover at the time of the response evaluation but there is otherwise no evidence of CLL otherwise, a repeat determination should be performed at the time of count recovery (polymorphonuclear leukocytes ≥ 1,500/μL, platelets > 100,000/μL) but should not exceed 6 months.
- Patients who fulfill the criteria for CR with the exception of a persistent cytopenia (CR with incomplete recovery, CRi) that is believed to be treatment related will be considered a CRi. As stated above, patients falling into this category should ideally undergo a repeat bone marrow when counts recover fully. If the bone marrow at this time reveals no CLL, these patients will be considered to be in complete remission at that time.
- Patients who fulfill the criteria of CR with exception of having bone marrow lymphoid CLL nodules will be considered a nodular PR (nPR), and assessed prospectively for similarity to outcome with CR.
- Patients who fulfill the criteria of CR with exception of not having a bone marrow biopsy performed will be considered a clinical CR.

13.1.2 Partial Response: Requires a ≥ 50% decrease in peripheral lymphocyte count from pre-treatment value, ≥ 50% reduction in lymphadenopathy of as many as 6 measurable lymph nodes, and/or ≥ 50% reduction in splenomegaly/hepatomegaly for a period of at least two months. Additionally, these patients must have one of the following:

- Polymorphonuclear leukocytes ≥ 1,500/μL or 50% improvement from pre-treatment value
- Platelets > 100,000/μL or 50% improvement from pre-treatment value
- Hemoglobin > 11.0 g/dL (untransfused) or 50% improvement from pre-treatment value

- Patients who meet the criteria for PR with the exception of having less than a 50% reduction in peripheral lymphocyte count will be considered a partial response except persistent lymphocytosis (PR-L). These patients should continue to be followed on therapy and response status updated if the lymphocyte count does decrease by ≥ 50%.

13.1.3 Progressive Disease: Because of the well-described lymphocytosis that occurs with ibrutinib, patients receiving ibrutinib will not be considered to have progressive disease if they have an increase in lymphocyte count without other disease related symptoms (increasing lymph nodes, splenomegaly, disease-associated constitutional symptoms). Progressive disease will be characterized by any one of the following events:

- An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter (in patients on Arm 1, or those on Arms 2 or 3 who are not receiving ibrutinib)
- ≥ 50% increase in the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one lymph node must be ≥ 2 cm), appearance of new palpable lymph nodes
- ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin, appearance of palpable hepatomegaly or splenomegaly which was not previously present
- Transformation to a more aggressive histology (i.e., Richter's syndrome or prolymphocytic leukemia with ≥ 56% prolymphocytes)
- The progression of any cytopenia defines disease progression (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels >2 g/dL or to < 10 g/dL, or by a decrease of platelet counts > 50% or to < 100,000/μL, which occurs at least 3 months after treatment, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells. During therapy, cytopenias cannot be used to define disease progression.

13.1.4 Stable Disease

Patients who do not fulfill the criteria for complete or partial response as defined above but do not exhibit progressive disease will be considered to have stable disease.

13.2 Treatment-Related Lymphocytosis

Similar to other agents targeting B-cell receptor signaling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood[47].

Upon initiation of treatment, a transient phase of increase in lymphocyte counts (i.e., ≥50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. This effect has also been observed in some patients (33%) with relapsed/refractory MCL treated with ibrutinib. This observed transient lymphocytosis is usually not associated with an adverse event 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 resolves within a median of 7.1 weeks in the MCL and 18.7 weeks in the CLL patients.

A substantial increase in the number of circulating lymphocytes (e.g., > 400,000/mcL) has been observed in a subset of patients. There have been isolated cases of leukostasis reported in patients treated with ibrutinib.

14.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

14.1 Duration of Treatment

14.1.1 CR, PR, or SD

Arm 1: Continue treatment for 6 cycles. Upon completing 6 cycles of treatment, Arm 1 patients will be followed (in Arm 1 observation) at least every 3 cycles until progression. In the event that bendamustine and rituximab are discontinued for reasons other than progression, and the patient would like the option to crossover to ibruitnib alone in the future, then the patient will be followed (in Arm 1 observation) at least every 3 cycles until progression. Patients with documented disease progression are eligible to cross over to single-agent ibrutinib upon documentation of disease progression. These patients will remain on ibrutinib and follow the study calendar until second disease progression. After a second progression, patients will go on to survival follow up, followed every 6 months until 10 years from initial Step 1 registration.

Arm 2: Continue treatment until disease progression, with patients followed at least every 3 cycles until progression. After documented progression, patients will go on to survival follow up, followed every 6 months until 10 years from Step 1 registration.

Arm 3: Continue rituximab until cycle 6, then continue ibrutinib until disease progression. Patients will be followed at least every 3 cycles until progression. After documented progression, patients will go on to survival follow up, followed every 6 months until 10 years from Step 1 registration.

14.1.2 Disease Progression:

Remove from protocol therapy any patient with rapid disease progression.

14.1.3 Follow Up Schedule

Patient follow up is based on 28-day cycles.

Patients on Arm 1 who complete 6 cycles of protocol treatment are required to be followed in Arm 1 observation (every 3 cycles beginning Day 1 of Cycle 6) until progression, at which point they may be eligible to crossover. See section 5.6 and 7.0 for more information.

Patients on Arm 1 who discontinue bendamustine and rituximab prior to completion of Cycle 6 for reasons other than progression should be followed in Arm 1 observation if they would like to opportunity to crossover at disease progression. Should patients receive another therapy, then they will go on to clinical follow-up as outlined in the below paragraph.

Patients who end treatment for reasons other than progression and subsequent treatment will go to clinical follow up (as outlined in Section 7.0), followed at least every 3 cycles from the date of discontinuation for up to 10 years from registration (Step 1).

Patients who progress or receive a subsequent treatment will go to survival follow up (see Data Submission Schedule on A041202 Alliance and CTSU study page), followed every 6 months from the date of discontinuation for 10 years from registration (Step 1).

Patients who withdraw prior to starting any protocol treatment (with or without progression) will go to survival follow up, followed every 6 months for up to 10 years in observation from registration (Step1).

14.1.4 Follow-up schedule for ineligible patients registered to the trial

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue per Section 7.0. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial and have started treatment with subsequent discontinuation of study treatment, the same data submission requirements are to be followed per Section 7.0.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline, off treatment, and post-treatment follow up (i.e., relapse, progression, and survival) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

14.2 Extraordinary Medical Circumstances

If at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair,
- Document the reason(s) for discontinuation of therapy,
- Follow the patient for survival or secondary malignancy until death.

15.0 STATISTICAL CONSIDERATIONS

15.1 Overview and Study Design

This is a randomized phase III trial designed to evaluate whether or not two different ibrutinib-based therapeutic regimens improve progression-free survival (PFS) over standard of care (bendamustine + rituximab) in previously untreated, older (age ≥ 65 years) CLL patients who are symptomatic and require therapy by the IWCLL guidelines. This study will not be blinded. Treatments that are standard for younger CLL patients such as fludarabine-based regimens are often not adequately tolerated in older patients. As described earlier, recent studies have shown that in these older patients, bendamustine + rituximab is a tolerable and moderately effective regimen with a median PFS of approximately 3 years. Fischer et al found an overall median PFS in all patients of 33.8 months, where about half of patients were <65 years old. In looking at PFS by age group, those >70 years old had a median PFS of 37.6 months vs. 33.9 months for those ≤70 years. Many different treatment regimens are given to previously untreated CLL patients, but the combination of bendamustine + rituximab (BR) can be considered a standard regimen in this patient population and the best control arm against which to test novel targeted therapies. In this trial, we will formally test the superiority of two ibrutinib-base regimens (ibrutinib alone and ibrutinib + rituximab) each against this standard of care bendamustine + rituximab treatment arm. In addition, we will also compare the two ibrutinib-based regimens with each other (i.e. ibrutinib alone vs. ibrutinib + rituximab).

Primary Endpoint: The primary endpoint for all of the treatment arms in this phase III trial is PFS, where this will be defined as the time from study entry to the time of documented disease progression or death. All randomized patients meeting the eligibility criteria will be evaluable for progression-free status by intention to treat. Given the overall indolent nature of this disease, PFS is a meaningful endpoint, and has been shown to effectively correlate with OS benefit as well, such as that seen in the German CLL8 study. [5]

Several secondary endpoints will also be evaluated in this study, including OS, time to progression, duration of response, ORR, CR, complete and nPR rate, MRD status, toxicity and tolerability, geriatric functional status and quality of life, and several correlative markers described below.

Randomization: Patients will be randomized using dynamic allocation procedures to three arms in a 1:1:1 manner: bendamustine + rituximab (BR) vs. ibrutinib (I) vs. ibrutinib + rituximab (IR). Randomization will be stratified on Rai stage (intermediate vs. high) and presence of high-risk FISH abnormalities (del(11q22.3) or del(17p13.1) vs. not). In addition, we will also stratify on ZAP-70 methylation status (methylated vs. not, using a 20% methylation cut point), which is hypothesized to be strongly associated with clinical outcomes in CLL.

Study Design: The randomized phase III clinical trial design to be utilized in this study is described below. As noted above, patients will be randomized to one of three treatment arms: a control arm (bendamustine + rituximab) vs. ibrutinib alone vs. ibrutinib + rituximab. In an effort to limit patients assigned to the control arm, randomization will be done in a 1:1:1 manner to the three arms above, respectively. With these three treatment arms, there are three planned comparisons: (1) bendamustine + rituximab vs. ibrutinib alone; (2) bendamustine + rituximab vs. ibrutinib + rituximab; and (3) ibrutinib alone vs. ibrutinib + rituximab. In the unlikely event that one or both of the ibrutinib-based regimens are discontinued early due to early sufficient evidence of futility against the bendamustine + rituximab arm, the third comparison will not be conducted.

The overall Type I error rate for this trial will be constrained at 0.05 and with 90% power for each of the one-sided tests of the ibrutinib-based regimens versus bendamustine plus rituximab and for the one-sided comparison of the ibrutinib alone versus ibrutinib plus rituximab arms.

To adjust for the multiple pairwise comparisons between the arms, we will use a Bonferroni correction with an overall constraint of the Type I error rate to 0.05. Since we will primarily be conducting two main comparisons of interest (BR vs. I and BR vs. IR), each comparison will have a Type I error constraint of 0.025. It is of interest to maximize efficiency by comparing each of these arms against the common control arm, bendamustine + rituximab. However, we recognize that the experimental treatment arms are similar and can be considered related (ibrutinib alone, ibrutinib + rituximab) and thus that we in fact need to control for these multiple pairwise comparisons in addition to controlling error spending associated with multiple looks at the data. Since the comparison of I vs. IR arms is only of interest if both of them are found to be superior to the BR control arm, we will constrain the Type I error rate for that comparison to 0.05. While we could use a more complex approach to correcting for our multiple comparisons that involves modeling joint distributions and involving step-up or step-down procedures, it was felt that the marginal gains in efficiency with slightly reduced sample sizes would not outweigh the complexity and multiple assumptions that would be required.

Another assumption that we have for this design is that the overall accrual will be about 15 patients per month. Based on data available for the bendamustine plus rituximab arm as well as recent data for current phase II trials of ibrutinib-based regimens, we have the following hypotheses for our comparisons of interest, assuming that these PFS distributions are exponentially distributed:

bendamustine + rituximab vs. ibrutinib alone

PFS 2-yr estimates: 0.61 vs. 0.75

PFS medians: 34 months vs. 58 months

hazard ratio = 0.586

bendamustine + rituximab vs. ibrutinib + rituximab

PFS 2-yr estimates: 0.61 vs. 0.85

PFS medians: 34 months vs. 102 months

hazard ratio = 0.33

(these are our assumptions for ibrutinib plus rituximab; however, we will have power to detect the same differential as with ibrutinib alone versus bendamustine plus rituximab)

ibrutinib vs. ibrutinib + rituximab

PFS 2-yr estimates: 0.75 vs. 0.85

PFS medians: 58 vs. 102 months

hazard ratio = 0.57

We recognize that these hypothesized differentials of interest between the standard of care arm versus the ibrutinib-based regimens are quite large; however, it is felt that these improvements in PFS are necessary in order to more likely translate to corresponding improvements in OS. Note that with the comparisons of bendamustine plus rituximab versus either of the ibrutinib regimens, it makes sense to use a one-sided test for this. In other words, in our testing we only care if the ibrutinib-based regimens are specifically superior to the bendamustine plus rituximab arm. For the ibrutinib alone versus ibrutinib plus rituximab comparison, a one-sided test will also be used to be able to detect if PFS is significantly improved with the addition of rituximab to ibrutinib. Based on all of these considerations and constraints, this proposed study requires a total of 498 evaluable patients. This translates to 166 patients required for each treatment arm. We will plan to over-accrue by about 5% for a total accrual goal of 523 patients.

15.2 Accrual time and study duration

Based on our experience with cooperative group trials (e.g. CALGB 10404) run in this previously untreated CLL patient population as well as our experience in trials with ibrutinib-based regimens, our expected monthly accrual rate is 15 patients per month, or equivalently about 180 patients per year. Since this study will not overlap with the other cooperative group trial (run through ECOG), we expect that this projected accrual rate is realistic. Therefore, we anticipate that this trial will require about 36 months to accrue the 523 patients required for this study. Overall, we will require a minimum of 24 months of follow up on all patients for a total study duration of about 60 months.

15.3 Analysis Plan

The primary endpoint of PFS will be compared in each of the planned pairwise comparisons as described above. Each of these efficacy analyses will utilize an intent-to-treat approach to the analyses, where patients will be analyzed in the arm to which they were randomized. Log-rank statistics will be used to compare the PFS distributions of the different treatment arms. The methods of Kaplan and Meier will be used to estimate PFS for the treatment arms. For each of the planned comparisons, we will assess the corresponding hazard ratios, 2-year PFS estimates, and PFS medians along with their 95% confidence intervals.

Note that patients who are randomized to the BR treatment arm will be allowed to cross over to receive ibrutinib therapy once they have documentation of progression. Since patients who are

allowed to cross over will have had the event of interest for evaluation of the primary endpoint, this will not comprise our primary endpoint of progression-free survival in these comparisons.

For each of the comparisons of BR vs. either of the ibrutinib regimens, we will conduct three interim evaluations, with the first planned interim analysis taking place after approximately 33% of events have occurred. After that, two more interim evaluations would be planned at 50% and 75% of the planned full information (events) for this study. If in these interim evaluations sufficient evidence (per criteria outlined below) is observed that an ibrutinib-based arm is superior to the BR arm, then accrual to the BR may be suspended and terminated. Patients would still continue to be randomized to ibrutinib vs. ibrutinib+rituximab to fully evaluate that comparison. For the interim analysis related to the comparison of I vs. IR, we expect that the study will be fully accrued prior to seeing 50% of events required to perform the first interim analysis. Any interim analyses related to this comparison will be done to primarily identify if there is overwhelming evidence that the addition of rituximab to ibrutinib produces significantly superior results in terms of PFS. To preserve the Type I error rate control for each of these comparisons on superiority, the Lan-DeMets error spending rate function with the O'Brien-Fleming boundaries is utilized. Futility boundaries have also been developed for the comparisons against control, where if at any of the planned interim analyses the hazard ratio is >1.05 in favor of the control arm, we will consult with the Alliance DSMB. If these boundaries are crossed, then the Alliance DSMB will determine if accrual to that arm should be suspended and/or if treatment of patients should be modified based on these results. The interim and final analysis boundaries and characteristics were generated using the East 5 clinical trial software program (version 5.4, Cytel Inc).

Bendamustine + Rituximab vs. Ibrutinib

Information fraction	Cumulative events	Alpha spent	Beta spent	Truncated boundary	Estimated analysis time (months)
0.33	53	0.0001	0.005	3.73	25
0.50	80	0.00153	0.0119	2.96	31
0.75	120	0.00965	0.0356	2.359	40
1.0	159	0.025	0.1	2.014	50

Ibrutinib alone vs. Ibrutinib + Rituximab

Information fraction	Cumulative events	Alpha spent	Beta spent	Boundary to reject H0	Estimated analysis time (months)
0.50	60	0.00557	0.0238	2.538	36
0.75	89	0.0236	0.0712	2.016	47
1.0	119	0.05	0.2	1.72	59

15.4 Secondary Endpoint Analysis Plan

Several secondary endpoints will be evaluated in the context of this proposed clinical trial.

Best achieved response will be assessed for each treatment arm after one year as well as after two years given the potential for late and/or improved responses. Response rates will be assessed in multiple ways, where we will focus on the proportion of patients who achieve a biopsy-proven complete response (CR) and the proportion of patients who achieve any response to treatment (ORR) where we include partial responses, CRs as well as nPRs. We will assess the CR+nPR rate since nPRs have been shown to have improved time to event outcomes. Additionally, we will evaluate the proportion of patients who attain MRD negative status at time of CR documentation and at 2 years. Response and MRD negative status will be calculated for each arm, and will be estimated using the number of patients with the type of response of interest

divided by the total number of patients randomized to that treatment arm and the number of patients who achieve minimal residual disease divided by the total number randomized to that treatment arm, respectively. Assuming that the incidence of each type of response (CR, overall, or CR/nPR) as well as incidence of MRD is binomially distributed, we will calculate corresponding exact binomial 95% confidence intervals for the true response and MRD rates. This will also be performed for the cross over arm proposed in an ancillary manner.

The Kaplan-Meier method will be used to estimate overall survival and time to progression distributions in this CLL population. Each of these variables will be measured from the date of registration to the date of the event (i.e., death or disease progression) or the date of last follow-up to evaluate that event. Patients who are event-free at their last follow-up evaluation will be censored at that time point. In addition, any patients who go on to subsequent therapy prior to disease progression will be censored at that time.

The Kaplan-Meier method will be used to estimate the duration of response in the CLL population. Duration of response is defined for all evaluable patients who have achieved an objective response (i.e., CR, nPR, PR) and will be calculated as the length of time from the date at which the patient's objective status is first noted to be a response to the date that progression or death is documented (if one has occurred) or to the date of last follow-up (for those patients who have not progressed or died). These evaluations will also be performed for the cross over arm proposed.

The Kaplan-Meier method will be used to estimate PFS and OS in patients who achieve a CR by two years, where we will assess differential PFS and OS based on MRD negative status at time of CR documentation. Additionally, at the 2-year time point, all responding patients will have MRD status evaluated. At both of these time points, hazard ratios and 95% confidence intervals for MRD negative versus positive patients will be calculated for PFS and OS.

Toxicity and Tolerability: Frequency and severity of adverse events and tolerability of the regimen in each of the treatment arms will be collected and summarized using descriptive statistics. As per NCI CTCAE v4.0, 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. The incidence of severe (grade 3+) adverse events or toxicities will be described. In particular, we will assess the proportion of patients who experience grade 3 or higher non-hematologic toxicity for each of the treatment arms. We will also assess tolerability of the regimens through assessing the number of patients who required dose modifications and/or dose delays. In addition, we will also capture the proportion of patients who go off treatment due to adverse reactions or even those who refuse further treatment for lesser toxicities that inhibit their willingness to continue participation on the trial. These tolerability measures will be assessed within each of the treatment arms and we will evaluate differences in these measures between the arms. All patients who have received at least one dose of any of the therapeutic agents in a treatment arm will be evaluable for toxicity and tolerability. This will also be performed for the cross over arm proposed.

Functional Status measures and correlative endpoint analyses will also be analyzed in the context of this trial. Descriptions of these analyses are provided in Sections 10.1 and 10.2.

15.5 Correlative Science Statistical Considerations

15.5.1 Statistical Considerations for A041202-LC1

The correlative markers will be summarized quantitatively and graphically between treatment arms. In particular, we will assess several known prognostic factors for CLL at baseline (cytogenetics, FISH abnormalities, IgVH mutational status, ZAP-70 methylation status), as well as new biomarkers that may arise with continued research, and how these factors relate to the primary endpoint of PFS and secondary endpoints, including response rate and OS. Since preliminary data on ibrutinib-based therapies suggest a low event rate, we will not only evaluate the differential distribution of these known prognostic factors for CLL using the log rank test for time to event data, but also in those who are progression-free at two years versus those who are not. Levels of difference that we are able to detect with at least 80% power will depend largely on the observed distribution of these factors in patients accrued on trial. Constraining overall Type I error to .05 and even with a Bonferroni correction for ten simultaneous comparisons, two-sided chi-square tests will have 80% power to detect differences of 20% or more in 2-year PFS rates (e.g. 65% vs. 85%, 73% vs. 90%), even with incidences of a factor as small as 25%. This is reasonable since it is expected that ~33% of patients will be identified as having ZAP-70 methylation >20%. Incidence rates of cytogenetic abnormality del(11q) are often near 25%, although incidence rates of del(17p) are typically lower (~8%), early studies with ibrutinib have shown quite favorable outcomes in this group of patients who typically do not respond to other treatment regimens and consequently, we anticipate that enrollment of patients in this high-risk group will be much higher and will not be a concern, similar to what we have seen in other trials with ibrutinib-based regimens. Likewise, we anticipate that patients with complex karyotype will be over-represented, in part because complexity is associated with presence of del(17p), but also because incidence of complexity tends to be associated with older age. Log rank tests for these factors will have 80% power to detect differences in PFS distributions corresponding to similar 2-year PFS estimates.

Not only will these markers be evaluated within each treatment arm, but they will also be evaluated in relation to progression-free survival across treatment arms through Cox regression models, adjusting for treatment arm in the model. We will also assess the impact of these factors and how they may affect other clinical outcomes of interest and if these differ based on treatment received. In addition to known prognostic factors in CLL, we will also evaluate other correlative markers in baseline samples and in samples collected at relapse. DNA mutation markers will be explored in relation to clinical outcomes of interest as well as how they may change from baseline to time of relapse. Assessments of minimal residual disease (MRD) will be used in patients classified as CR to further evaluate their status as disease-free and if this further impacts their ability to remain progression-free and alive. Overall, given that this is a hematologic malignancy with accessible “tumor”, we expect to obtain evaluable samples on at least 90% of patients.

For gene expression profiling and miR analysis by nanostring, baseline samples for patients in each treatment arm will be evaluated in relation to their progression-free status at 2 years to assess differential expression in those who achieve this clinical outcome of interest vs. those who do not. In addition, we will also assess achievement of CR by two years vs. not and identify those markers that have differential expression between these outcome groups. Both mRNA and miR expression data will be normalized and summarized using log base 2 expression values for further analysis. A filtering step will be performed to remove probe sets/miRs for which the majority of expression values are below a noise level cutoff. Standard statistical methods (i.e. two-sided two-sample t-tests) will be used to determine differentially expressed genes and miRNAs, although we will make a correction for multiple

comparisons (using a univariate significance level of α=0.001 for gene expression and α=0.005 for miR expression to control the average number of false positives when screening across all probe sets and miRNAs). In analyses that focus on a short list of genes or miRNAs, identified apriori to have potential impact in CLL through previous work by our group (e.g. miR-155, miR-29c), there is at least 80% power to detect 1.5-fold changes in expression, assuming 85% of patients within a treatment arm are progression-free, a CV=0.5, and constraining overall Type I error to .05 with a Bonferroni correction for ten simultaneous comparisons. If the CV is as large as 1.0 for some genes/miRNAs, 2-fold changes can be detected with at least 80% power. In addition, we will evaluate changes in miR marker expression levels in pre- vs. post-treatment samples in those treated on the ibrutinib alone treatment arm, and how these changes may differ based on achievement of clinical outcomes of interest as well as between patients with vs. without persistent lymphocytosis. It is anticipated that approximately 20-25% of patients treated with single-agent ibrutinib will have persistent lymphocytosis at 9 months, resulting in approximately 35 paired samples to be screened for markers of resistance. With n=35, there is at least 80% power to detect 1.65 fold or 1.55 fold changes, respectively, for any gene or miRNA with CV<0.5; 2.40 or 2.15 fold changes with CV<1.0 can be detected with at least 80% power for any gene or miRNA, respectively. These calculations allow for 1 false positive per 1000 features with gene expression data (i.e. α=0.001) and 5 false positive per 1000 features with miRNA data (i.e. setting α=0.005). Changes in miR marker expression from baseline to time of relapse will also be evaluated in all patients on either of the ibrutinib-based treatment arms who relapse.

Finally, we will evaluate whether local FISH analysis is concordant with centralized FISH analysis for del(11q22.3) and del(17p13.1); i.e. each of these chromosomal abnormalities will be evaluated using FISH both locally and centrally at baseline, and the results will be compared for each patient. Since we are primarily interested in classification of having this abnormality vs. not, we will use a Kappa test to assess agreement of this classification for del(11q22.3) and del(17p13.1) for the local vs. centralized assessment. As noted earlier, based on our past experience with trials that include ibrutinib we expect that the rate of CLL patients with del(17p13.1) will be higher than what we typically see in CLL trials If we assume that we will see 25% of patients with the abnormality of interest, we will have at least 90% power to detect a significant difference from a near perfect concordance (H0: kappa=0.99) if the true Kappa is actually 0.96 or lower. Even if the rate of patients with del(17p13.1) is lower (10%), then we will still have 80% power to detect a significantly different rate of concordance if the true Kappa is 0.95 or lower.

15.5.2 Statistical Considerations for A041202-EL1

15.5.2.1 Objective 1: To describe the baseline functional status, comorbid medical conditions, and number of medications of older CLL patients who meet criteria for therapy

The baseline measures for each of the components of the geriatric assessment will be summarized for the entire group of patients enrolled on the trial and for whom a geriatric assessment was completed as well as for each arm individually. The values among the arms will be compared to assess for the clinical and statistical differences. It is possible that imbalances can occur because the geriatric assessment is optional and so original randomization of the patients might be jeopardized. Categorical values will be compared with a chi-square test and continuous values will be compared with an ANOVA (if the distribution of the measurements is sufficiently normal) or a Kruskal-Wallis test (if the distribution of measurements is considerably skewed).

15.5.2.2 Objective 2: To determine how functional status changes with therapy using baseline to 6 month evaluation and end-of-study/2 year evaluation; to determine whether this change is different among the treatment groups

This analysis will use the instruments that assess functional status: OARS MFAQ (IADL), MOS physical functioning, Karnofsky performance status rated by a health care professional, Karnofsky performance status rated by the patient, timed "Up and Go", and number of falls in the last six months. For each measure and each patient, we will compute the differences at 6 months compared to baseline (6mo-B) and the differences at 2-years compared to baseline (2yr-B). These changes will be summarized with descriptive statistics and graphs for each arm. The first analysis will be to determine whether there was a change observed for each measure within a treatment arm. This will be determined by the Wilcoxon signed-rank test for each arm for continuous variables and McNemar's test for categorical variables. We will do this for the 6-month endpoint and for the 2-year endpoint. The next analysis will be to determine whether the magnitude of the changes from baseline differ among the different treatment groups. This will be done using a Wilcoxon-Mann-Whitney test for continuous/ordinal values and a Fisher's exact test or chi-square test for dichotomous variables. A secondary analysis will be to do a comparison of 6mo-B and 2yr-B values between the subgroups of patients who are in remission at the end of 2 years and those who had progressed prior to 2 years. These comparisons will be made within each treatment arm as well as between treatment arms. There will be multiple comparisons made as part of the analysis plan for this aim and so we will make a partial correction. Specifically, we will not make a full Bonferroni correction but rather will reduce the level of significance from 0.05 to 0.01. In other words, differences will only be considered to be statistically significant for this aim if the p-value is less than 0.01. We feel this is appropriate because the intent of this aim is primarily exploratory.

15.5.2.3 Objective 3: To determine whether geriatric assessment variables known to be associated with chemotherapy toxicity in other disease groups can also predict therapy-associated toxicity in the CLL population

Detailed descriptions of hypotheses, expected sample sizes, power calculations and analysis plans for these objectives can be found in Section 10.2.3.

15.5.3 Statistical Design for A041202-PP1 (Evaluation of Candidate Pharmacogenetic Determinants of Ibrutinib or Ibrutinib/Rituximab Response)

The primary statistical objective for this study is to investigate the relationship between the *FCGR3A* SNP (rs396991) and response. The response phenotype will be quantified using MRD negativity status. We specifically hypothesize that in the rituximab-containing arms the T/T homozygotes will have a lower probability of achieving MRD negativity compared to the patients who have at least one copy of the G allele. We will use the Cochran–Mantel–Haenszel statistic, stratified by treatment arm, assuming no third order interaction.

The proposed clinical study aims to enroll a total of 523 patients. The primary analyses will be restricted to patients who self-report as non-Hispanic whites. Our previous genome-wide association studies have shown this to be a good surrogate marker for identifying a genetic European subset. We expect that 85% of patients registered the study will self-report as non-Hispanic whites. We also expect that 85% of the patients will consent and usable samples to pharmacogenomic studies. The minimum expected sample size will be 377. We will genotype any patient who provides consent and a usable sample.

The relative allelic frequencies for rs396991 are highly variable in different racial groups (G is the minor allele in Africans and T is the minor allele in Asians). The relative genotypic frequencies for rs396991, assuming the study population is a similar population as in the NHLBI Exome Sequencing Project, are predicted to be: 0.12 G/G, 0.41 G/T, 0.47 T/T.

For the power calculation, we will assume that the relative genotypic frequencies for the two groups are 0.47 (T/T) and 0.53 (G/T or G/G). We also assume that the response rates are 0.3 and 0.1 in arms 1 and 3 respectively. Within each arm, the MRD negativity will be expressed as the mixture piD=p0*0.47+p0*D*0.53 where p0 is the probability of achieving MRD negativity for the T/T group in this arm. The power, at the two-sided 0.05 level, is 0.8 for D=2.05.

As an exploratory analysis, we will consider genotype by rituximab interaction with respect to response. This will be carried out using a multiplicative logistic regression model incorporating all three arms. We will also consider using other clinical outcomes (e.g., outcome, toxicity) as phenotypes. We will also consider molecular markers assayed on these patients as phenotypes (e.g., eQTLs).

In addition, we may use the DNA collected to consider other candidate SNPs or to conduct a genome-wide association study (GWAS) to validate other or identify novel candidates, or, as next generation sequencing platforms become more cost effective, consider exome or whole-genome sequencing.

15.6 Inclusion of Women and Minorities

It is the intent of the Alliance to enroll patients regardless of gender or race. Both men and women of all races and ethnic groups are eligible for this study. In the development of this protocol, the possibility of inherent gender or racial/ethnic differences in treatment response has been considered.

Accrual Targets					
	Sex/Gender				
Ethnic Category	**Females**		**Males**		**Total**
Hispanic or Latino	11	+	18	=	29
Not Hispanic or Latino	163	+	331	=	494
Ethnic Category: Total of all subjects	174	+	349	=	523
Racial Category					
American Indian or Alaskan Native	1	+	1	=	2
Asian	1	+	3	=	4
Black or African American	12	+	24	=	36
Native Hawaiian or other Pacific Islander	3	+	1	=	4
White	157	+	320	=	477
Racial Category: Total of all subjects	174	+	349	=	523

15.7 CDUS Reporting

The Alliance Statistical Data Center will submit quarterly reports to CTEP by electronic means using the Clinical Data Update System (CDUS).

16.0 EXPEDITED ADVERSE EVENT REPORTING AND COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS

16.1 Expedited Adverse Event Reporting

Investigators are required by Federal Regulations to report serious adverse events as defined below. Alliance investigators are required to notify the Investigational Drug Branch (IDB), the Alliance Central Protocol Program Office, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. All such events must be reported in an expedited manner using the CTEP Adverse Event Reporting System (CTEP-AERS). The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Be sure to read this entire protocol section, as requirements are described in both the table and bullet points following the table below. Note that the additional instructions or exclusions are protocol specific, and in the case of a conflict, the additional instructions or exclusions supersede the table.

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

A041202: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Treatment[1,]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

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)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

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).

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.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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

Expedited AE reporting timelines are defined as:

- "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.

[1]Serious adverse events that occur more than 30 days after the last treatment require reporting as follows:

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

- All Grade 4, and Grade 5 AEs that are at least possibly related to treatment

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization, and that are at least possibly related to treatment.
- Grade 3 adverse events that are at least possibly related to treatment.

Effective Date: May 5, 2011

Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 3 Trials Utilizing an Agent Under an IND:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB, according to local IRB policies.
- Alliance A041202 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.
- Treatment expected adverse events include those listed in Section 11.0, in the package inserts for bendamustine and rituximab, and in the CAEPR for ibrutinib (see Section 16.2, below). **Note** that the ASAEL column of the CAEPR for ibrutinib has been replaced with the specific protocol exceptions to expedited reporting (SPEER) list. This list now includes "expected" severity grades in addition to event terms.
- All suspected and confirmed cases of fungal infections should be reported to CTEP within 24 hours.
- All new malignancies must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), and *in situ* tumors. In CTCAE version 5.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy or (4) Neoplasms benign, malignant and unspecified-other. Whenever possible, the CTEP-AERS reports for new malignancies should include, tumor pathology, history of prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

- All pregnancies and suspected pregnancies occurring in female patients during therapy or within 90 days after completion of treatment on A041202 must be reported via CTEP-AERS. Use the event term "pregnancy, puerperium, or perinatal condition-other, fetal exposure (grade 4)."
  - CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities). In CTCAE v5.0, pregnancy loss is defined as "Death in utero," and any pregnancy loss should be reported expeditiously as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC as currently CTEP-AERS recognizes this event as a patient death.
  - The CTEP-AERS report should be amended for any neonatal deaths or complications occurring within 30 days of birth independent of attribution. Infant deaths occurring after 30 days considered to be related to in utero exposure to the agents used in this trial should be reported via CTEP-AERS. A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.
- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g., cooperative group data reporting (see Section 6.1).

16.2 Comprehensive Adverse Events and Potential Risks (CAEPR)

16.2.1 Ibrutinib (PCI-32765, NSC # 748645)

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/aeguidelines.pdf for further clarification. *Frequency is provided based on 2082 patients.* Below is the CAEPR for Ibrutinib (PCI-32765).

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 2.6, January 29, 2018[1]

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		***Anemia (Gr 3)***

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 - 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			***Diarrhea (Gr 3)***
	Mucositis oral		
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
	Fatigue		***Fatigue (Gr 3)***
	Fever		
		Sudden death NOS	
HEPATOBILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
	Infection[3]		***Infection[3] (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		

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%)**	
	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		
		Pneumonitis[6]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Skin and subcutaneous tissue disorders - Other (angioedema)[7]	
	Skin and subcutaneous tissue disorders - Other (rash)[8]		***Skin and subcutaneous tissue disorders - Other (rash)[8] (Gr 3)***
		Stevens-Johnson syndrome	
VASCULAR DISORDERS			
	Hypertension		
		Hypotension	
	Vascular disorders - Other (hemorrhage)[9]		

[1]This 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.

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

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

[4]Fungal 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.

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

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

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

[8]Rash may include but is not limited to the terms dermatitis, erythema, rash generalized, rash maculo-papular, rash pustular, rash pruritic, and urticaria.

[9]It 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 limitied 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
HEPATOBILIARY 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.

16.3 Adverse Event List for Commercial Agents

For a complete list of adverse events and potential risks for rituximab and bendamustine, please refer to the FDA-approved package labeling for both drugs.

16.3.1 Rituximab

The most serious adverse events associated with rituximab include severe infusion reactions, tumor lysis syndrome, and severe mucocutaneous reactions. Severe infusion reactions consisting of hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock may be fatal. Most reported fatal reactions occurred within 24 hours of the first dose of rituximab. Because severe infusion reactions have been noted more frequently in patients with high leukocyte counts, such patients should be observed closely.

Tumor lysis syndrome resulting in renal failure has been described, and occasional fatalities noted. Tumor lysis syndrome is more likely in patients with high numbers of circulating malignant cells.

Severe mucocutaneous reactions associated with rituximab include Stevens-Johnson syndrome and toxic epidermal necrolysis. The onset of these reactions has been from 1-3 weeks.

Less severe infusion reactions are common with rituximab. These include fever, chills, and dyspnea. The mechanism of rituximab infusion reactions is thought to be the release of cytokines. If a reaction occurs, the infusion should be stopped until the symptoms resolve, and then restarted at a 50% slower rate. Consider additional pre-medication with acetaminophen 650 mg PO and diphenhydramine 50 mg PO/IV (or equivalent antihistamine).

Recent reports describe hepatitis B reactivation with fulminant hepatitis, hepatic failure and death in some patients with hematologic malignancies treated with rituximab. The majority of these patients received rituximab in combination with chemotherapy. The median time to diagnosis of hepatitis was approximately 4 months after starting rituximab and approximately 1 month after the last dose.

Exacerbation or reactivation of other viral infections has also been reported with rituximab. Recent reports describe JC virus reactivation leading to progressive multifocal leukoencephalopathy (PML) in patients who were receiving rituximab. Patients presenting with new neurologic findings (e.g., major changes in vision, unusual eye movements, loss of balance or coordination, confusion) should be evaluated for PML.

A report in the literature described an increase in fatal infection in HIV-related lymphoma patients when rituximab was used in combination with CHOP chemotherapy, as compared to CHOP alone.

16.3.2 Bendamustine

The most common side effect is bone marrow suppression. The most common non-hematologic adverse events in CLL (>15%) include pyrexia, nausea, and vomiting. Other adverse reactions seen frequently include asthenia, fatigue, malaise/weakness, dry mouth, somnolence, cough, constipation, headache, mucosal inflammation, and stomatitis.

16.4 Events of Special Interest

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the Sponsor. These events will be reported to the Sponsor **via CTEP-AERS** within 24 hours of awareness following the procedure described above for SAEs and will require enhanced data collection. **All Events of Special Interest will be submitted within 24 hours of awareness even if they do not meet serious criteria.**

Major Hemorrhage

Major hemorrhage is defined as any of the following:

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

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

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APPENDIX I PATIENT MEDICATION DIARY

Today's date _____ **Agent: Ibrutinib**

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **ibrutinib**.
2. You will take **ibrutinib** on days 1-28.
3. Record the date, the number of capsules of each size you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
5. Take ibrutinib at least 30 minutes before eating or at least 2 hours after a meal. The capsules are not meant to be opened or dissolved. If you miss a dose, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Do not take extra capsules to make up a missed dose.
6. Please return this form and the bottle with any leftover capsules to your physician when you go for your next appointment.

Day	Date	Time of dose	# of capsules taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				

Day	Date	Time of dose	# of capsules taken	Comments
21				
22				
23				
24				
25				
26				
27				
28				

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study _____
3. Patient's dose cohort _____
4. Total number of capsules taken this month (each size) _____
5. Physician/Nurse/Data Manager's Signature _____

Patient's signature

_____

APPENDIX II INDUCERS AND INHIBITORS CYP3A4/5

A strong inhibitor is one that causes a >5-fold increase in plasma AUC values or >80% decrease in clearance. **Strong inducers and inhibitors are in bold.**

CYP3A4/5 inducers	CYP3A4/5 inhibitors
Efavirenz	**Cyclosporine**
Nevirapine	**Indinavir**
	Miconazole
Barbiturates	**Nelfinavir**
Carbamazepine	**Poscanazole**
Glucocorticoids	**Ritonavir**
Modafinil	**Clarithromycin**
Oxcarbazepine	**Itraconazole**
Phenobarbital	**Ketoconazole**
Phenytoin	**Nefazodone**
Pioglitazone	**Saquinavir**
Rifabutin	**Telithromycin**
Rifampin	**Voriconazole**
St. John's wort	
Troglitazone	Aprepitant
	Atazanavir
	Caffeine
	Clotrimazole
	Conivaptan
	Cimetidine
	Delavirdine
	Desipramine
	Diltiazem
	Efavirenz
	Erythromycin
	Fluconazole
	Fosaprepitant
	Grapefruit juice
	Haloperidol
	Isoniazid
	Metronidazole
	Nicardipine
	Norfloxin
	Quinidine
	Tetracycline
	Verapamil

APPENDIX III REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and recorded on the Registration Fatigue/Uniscale Assessments Form (see Forms Packet).

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

A translator may be used to administer the assessment. Additionally, since CCTG is participating in A041202, a French version of the assessment has been provided on the following page.

How would you describe:
your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

Fatigue/Uniscale Évaluation

Instructions: S'il vous plaît, pour chaque article ci-dessous, encerclez le numéro (0-10) qui vous décrit le mieux.

Comment décririez-vous :

1. Votre niveau de fatigue moyen au cours de la dernière semaine, aujourd'hui inclus?

0	1	2	3	4	5	6	7	8	9	10
Aucune fatigue										La pire fatigue possible

2. Votre qualité de vie globale dans la semaine écoulée, y compris aujourd'hui?

0	1	2	3	4	5	6	7	8	9	10
Aussi mauvaise que possible										Aussi bonne que possible

APPENDIX IV COLLABORATIVE AGREEMENTS PROVISIONS

The ibrutinib supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between Pharmacyclics (hereinafter referred to as "Collaborator") 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/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Ibrutinib may not be used for any purpose outside the scope of this protocol, nor can ibrutinib be transferred or licensed to any party not participating in the clinical study. Collaborator data for ibrutinib are confidential and proprietary to Collaborator and shall be maintained as such by the investigators. The protocol documents for studies utilizing 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 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 NCI, 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 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 Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). 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 by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies 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:

   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.

APPENDIX V GERIATRIC ASSESSMENT (A041202-EL1) MEASURES

A Randomized Phase III Study of Bendamustine Plus Rituximab Versus Ibrutinib Plus Rituximab Versus Ibrutinib Alone in Untreated Older Patients with Chronic Lymphocytic Leukemia (CLL)

Self Assessment Measure - Patient Questionnaire

Assessment Period

- ☐ Prior to Treatment (between pre-registration and start of cycle 1)
- ☐ Day 1 of Cycle 6
- ☐ Progression or 2 years

Responsible person name (*Physician, Nurse, or CRA*) _____

Date Completed: *(mm/dd/yyyy)* __ __/__ __/__ __ __ __ Patient Study ID Number: _____

Patient Initials: _____
L F M

Study Number: A041202

PATIENT INFORMATION SHEET
Patient Completed – Patient Questionnaire

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet is to be completed prior to your first treatment, on day 1 of cycle 6, and at progression or 2 years.

2. The booklet contains 12 set of questions:
    a. Background information
    b. Daily activities questionnaire
    c. Physical activities questionnaire
    d. Current health rating questionnaire
    e. Falls questionnaire
    f. Your health questionnaire
    g. Mental Health questionnaire
    h. Social activities questionnaire
    i. Social support questionnaire
    j. Spirituality/religion questionnaire
    k. Your feelings questionnaire
    l. Questions concerning the questionnaire

3. Directions on how to complete each set of questions are written on the top of the page.

4. You may call a member of the study team to answer any questions you might have. You will be given a name and telephone number. You can call anytime with any concerns or questions

5. Bring the booklet with you to your next clinical visit. It is very important that you return the booklet to us, whether you finish the study or not.

Thank you for taking the time to help us.

PATIENT INFORMATION SHEET
Patient Completed – Patient Questionnaire

Patient Instructions: If you are unable to complete the questionnaire, a member of your health care team will assist you. Please do not have a family member complete the questionnaire for you.

A. BACKGROUND INFORMATION

1. What is the highest grade you finished in school? *(Mark one with an X).*
   - ☐ 8th grade or less
   - ☐ 9-11th grade
   - ☐ High school graduate/GED
   - ☐ Associate degree/some college
   - ☐ Vocational/technical school
   - ☐ Bachelor's degree
   - ☐ Advanced degree
   - ☐ I prefer not to answer

2. What is your marital status? *(Mark one with an X.)*
   - ☐ Married
   - ☐ Domestic partnership
   - ☐ Widowed
   - ☐ Divorced
   - ☐ Separated
   - ☐ Never married
   - ☐ I prefer not to answer

3. With whom do you live? *(Mark all that apply with an X.)*
   - ☐ Spouse / partner
   - ☐ Girlfriend / boyfriend
   - ☐ Children aged 18 years or younger
   - ☐ Children aged 19 years or older
   - ☐ Parent(s)/ parent(s)-in-law
   - ☐ Live alone
   - ☐ Other specify _____
   - ☐ Other relative specify _____

4. What is your current employment status? *(Mark one with an X.)*
   - ☐ Employed 32 hours or more per week
   - ☐ Employed less than 32 hours per week
   - ☐ Homemaker
   - ☐ Disabled
   - ☐ On medical leave
   - ☐ Unemployed
   - ☐ Retired
   - ☐ Full-time student
   - ☐ Part-time student
   - ☐ Other specify _____

B. DAILY ACTIVITIES*

PATIENT INSTRUCTIONS: Indicate your response by marking an X in one box per question.

1. Can you use the telephone…
   - ☐ without help, including looking up and dialing;
   - ☐ with some help (can answer phone or dial operator in an emergency, but need a special phone or help in getting the phone number or dialing); or
   - ☐ are you completely unable to use the telephone?
2. Can you get to places out of walking distance…
   - ☐ without help (can travel alone on buses, taxis, or drive your own car);
   - ☐ with some help (need someone to help you or go with you when traveling); or
   - ☐ are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?
3. Can you go shopping for groceries or clothes (assuming you have transportation) …
   - ☐ without help (taking care of all shopping needs yourself, assuming you have transportation);
   - ☐ with some help (need someone to go with you on all shopping trips); or
   - ☐ are you completely unable to do any shopping?
4. Can you prepare your own meals…
   - ☐ without help (plan and cook full meals yourself);
   - ☐ with some help (can prepare some things but unable to cook full meals yourself); or
   - ☐ are you completely unable to prepare any meals?
5. Can you do your housework…
   - ☐ without help (can clean floors, etc);
   - ☐ with some help (can do light housework but need help with heavy work); or
   - ☐ are you completely unable to do any housework?
6. Can you take your own medicines…
   - ☐ without help (in the right doses at the right time);
   - ☐ with some help (able to take medicine if someone prepares it for you and/or reminds you to take it); or
   - ☐ are you completely unable to take your medicines?
7. Can you handle your own money…
   - ☐ without help (write checks, pay bills, etc.);
   - ☐ with some help (manage day-to-day buying but need help with managing your checkbook and paying your bills); or
   - ☐ are you completely unable to handle money?

* OARS IADL – Fillenbaum, G.G. and Smyer, M.A., 1981

Self Assessment Measure – Patient Questionnaire

C. PHYSICAL ACTIVITIES*

1. The following items are activities you might do during a typical day. Does your health limit you in these activities? **(*Mark an X in the box on each line that best reflects your situation.*)**

Activities	Limited a lot	Limited a little	Not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
c. Lifting or carrying groceries	☐	☐	☐
d. Climbing several flights of stairs	☐	☐	☐
e. Climbing one flight of stairs	☐	☐	☐
f. Bending, kneeling, or stooping	☐	☐	☐
g. Walking more than a mile	☐	☐	☐
h. Walking several blocks	☐	☐	☐
i. Walking one block	☐	☐	☐
j. Bathing or dressing yourself	☐	☐	☐

* MOS, Physical Functioning Scale – Stewart, A.L. and Ware, J.E., 1992

D. CURRENT HEALTH RATING*

Which one of the following phrases best describes you at this time? *(Mark one with an X.)*

- ☐ Normal, no complaints, no symptoms of disease
- ☐ Able to carry on normal activity, minor symptoms of disease
- ☐ Normal activity with effort, some symptoms of disease
- ☐ Care for self, unable to carry on normal activity or do active work
- ☐ Require occasional assistance but able to care for most of personal needs
- ☐ Require considerable assistance for personal care
- ☐ Disabled, require special care and assistance
- ☐ Severely disabled, require continuous nursing care

* Patient KPS – Loprinzi, C.L., et al., 1994

E. FALLS

How many times have you fallen in the last 6 months? __ __ __

F. YOUR HEALTH

1. Your General Health*

Patient Instructions: Do you have any of the following illnesses at the present time, and if so, how much does it interfere with your activities: **Not at All, A Little or A Great Deal?** *(Mark an X in the box that best reflects your answer.)*

		If you have this illness: How much does it interfere with your activities?			
Illness	**No**	**Yes**		**Not at all**	**A little**	**A great deal**
a. Other cancers or leukemia	☐	☐	→	☐	☐	☐
b. Arthritis or rheumatism	☐	☐	→	☐	☐	☐
c. Glaucoma	☐	☐	→	☐	☐	☐
d. Emphysema or chronic bronchitis	☐	☐	→	☐	☐	☐
e. High blood pressure	☐	☐	→	☐	☐	☐
f. Heart trouble	☐	☐	→	☐	☐	☐
g. Circulation trouble in arms or legs	☐	☐	→	☐	☐	☐
h. Diabetes	☐	☐	→	☐	☐	☐
i. Stomach or intestinal disorders	☐	☐	→	☐	☐	☐
j. Osteoporosis	☐	☐	→	☐	☐	☐
k. Liver disease	☐	☐	→	☐	☐	☐
l. Kidney disease	☐	☐	→	☐	☐	☐
m. Stroke	☐	☐	→	☐	☐	☐
n. Depression	☐	☐	→	☐	☐	☐

* OARS IADL – Fillenbaum, G.G. and Smyer, M.A., 1981

2. How is your eyesight (with glasses or contacts)? *(Mark one with an X.)*
   - ☐ Excellent
   - ☐ Good
   - ☐ Fair
   - ☐ Poor
   - ☐ Totally blind

3. How is your hearing (with a hearing aid, if needed)? *(Mark one with an X.)*
   - ☐ Excellent
   - ☐ Good
   - ☐ Fair
   - ☐ Poor
   - ☐ Totally deaf

4. Do you have any other physical problems or illnesses *(other than listed in questions 1-4)* at the present time that seriously affect your health?
   - ☐ No
   - ☐ Yes *(If yes),* specify _____

   (If yes), how much does this interfere with your activities? *(Mark one with an X.)*
   ☐ Not at all ☐ Somewhat ☐ A great deal

* OARS IADL – Fillenbaum, G.G. and Smyer, M.A., 1981

Self Assessment Measure – Patient Questionnaire

G. MENTAL HEALTH QUESTIONNAIRE*

INSTRUCTIONS: These questions are about how you have been feeling within the past month. Please mark an "X" in the box on each line that best reflects your situation.

How much of the time during the past month:	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
1. has your daily life been full of things that were interesting to you?	☐	☐	☐	☐	☐	☐
2. did you feel depressed?	☐	☐	☐	☐	☐	☐
3. have you felt loved and wanted?	☐	☐	☐	☐	☐	☐
4. have you been a very nervous person?	☐	☐	☐	☐	☐	☐
5. have you been in firm control of your behavior, thoughts, emotions, feelings?	☐	☐	☐	☐	☐	☐
6. have you felt tense or "high-strung"?	☐	☐	☐	☐	☐	☐
7. have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
8. have you felt emotionally stable?	☐	☐	☐	☐	☐	☐
9. have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
10. have you felt restless, fidgety, or impatient?	☐	☐	☐	☐	☐	☐
11. have you been moody, or brooded about things?	☐	☐	☐	☐	☐	☐
12. have you felt cheerful, lighthearted?	☐	☐	☐	☐	☐	☐
13. have you been in low or very low spirits?	☐	☐	☐	☐	☐	☐
14. have you been a happy person?	☐	☐	☐	☐	☐	☐
15. did you feel you had nothing to look forward to?	☐	☐	☐	☐	☐	☐
16. have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
17. have you been anxious or worried?	☐	☐	☐	☐	☐	☐

* MHI-17 – Stewart, A.L. and Ware, J.E., 1992

H. SOCIAL ACTIVITIES*

1. During the past 4 weeks, how much time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
   (Mark one with an X.)

   ☐ All of the time
   ☐ Most of the time
   ☐ Some of the time
   ☐ A little of the time
   ☐ None of the time

2. Compared to your usual level of social activity, has your social activity during the past 6 months decreased, stayed the same, or increased because of a change in your physical or emotional condition?
   (Mark one with an X.)

   ☐ Much less socially active than before
   ☐ Somewhat less socially active than before
   ☐ About as socially active as before
   ☐ Somewhat more socially active as before
   ☐ Much more socially active than before

3. Compared to others your age, are your social activities more or less limited because of your physical health or emotional problems? *(Mark one with an X.)*

   ☐ Much more limited than others
   ☐ Somewhat more limited than others
   ☐ About the same as others
   ☐ Somewhat less limited than others
   ☐ Much less limited than others

* MOS, Social Activities – Stewart, A.L. and Ware, J.E., 1992

I. SOCIAL SUPPORT*

INSTRUCTIONS: People sometimes look to others for companionship, assistance or other types of support. How often is each of the following kinds of support available to you if you need it? (*Mark an X in the box on each line that best reflects your situation.*)

	None of the Time	A Little of the Time	Some of the Time	Most of the Time	All of the Time
1. Someone to help you if you were confined to bed.	☐	☐	☐	☐	☐
2. Someone you can count on to listen to you when you need to talk.	☐	☐	☐	☐	☐
3. Someone to give you good advice about a crisis.	☐	☐	☐	☐	☐
4. Someone to take you to the doctor if you needed it.	☐	☐	☐	☐	☐
5. Someone to give you information to help you understand a situation.	☐	☐	☐	☐	☐
6. Someone to confide in or talk to about yourself or your problem.	☐	☐	☐	☐	☐
7. Someone to prepare your meals if you were unable to do it yourself.	☐	☐	☐	☐	☐
8. Someone whose advice you really want.	☐	☐	☐	☐	☐
9. Someone to help you with daily chores if you were sick.	☐	☐	☐	☐	☐
10. Someone to share your most private worries and fears with.	☐	☐	☐	☐	☐
11. Someone to turn to for suggestions about how to deal with a personal problem.	☐	☐	☐	☐	☐
12. Someone who understands your problems.	☐	☐	☐	☐	☐

* MOS Social Support Survey – Sherbourne, C.D. and Stewart, A.L., 1991

J. SPIRITUALITY/RELIGION*

Directions: Please answer the following questions about your religious beliefs and/or involvement. (Please mark an "X" in the box on each line that best reflects your situation.)

1. How often do you attend church, synagogue, or other religious meetings? *(Mark one with an X.)*
   - ☐ More than once per week
   - ☐ Once a week
   - ☐ A few times a month
   - ☐ A few times a year
   - ☐ Once a year or less
   - ☐ Never

2. How often do you spend time in private religious activities, such as prayer, meditation or Bible study? *(Mark one with an X.)*
   - ☐ More than once a day
   - ☐ Daily
   - ☐ Two or more times per week
   - ☐ Once a week
   - ☐ A few times a month
   - ☐ Rarely or never

The following section contains 3 statements about religious belief or experience. Please mark the extent to which each statement is true or not true for you.

3. In my life, I experience the presence of the Divine (i.e., God). *(Mark one with an X.)*
   - ☐ Definitely true of me
   - ☐ Tends to be true
   - ☐ Unsure
   - ☐ Tends *not* to be true
   - ☐ Definitely *not* true

4. My religious beliefs are what really lie behind my whole approach to life. *(Mark one with an X.)*
   - ☐ Definitely true of me
   - ☐ Tends to be true
   - ☐ Unsure
   - ☐ Tends *not* to be true
   - ☐ Definitely *not* true

5. I tried hard to carry my religion over into all other dealings in my life. *(Mark one with an X.)*
   - ☐ Definitely true of me
   - ☐ Tends to be true
   - ☐ Unsure
   - ☐ Tends *not* to be true
   - ☐ Definitely *not* true

* DUREL: Duke University Religion Index – Koenig et al., 1997

K. YOUR FEELINGS*

1. Do you often feel sad or depressed? *(Mark one with an X.)*

☐ No ☐ Yes

2. How would you describe your level of anxiety, on the average? Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.

0	1	2	3	4	5	6	7	8	9	10
No anxiety										Anxiety as bad as it can be

* Mahoney et al., 1994; LASA – Locke et al., 2007

L. QUESTIONS CONCERNING THE QUESTIONNAIRE

1. Were there any questions difficult to understand? ☐ No ☐ Yes
   (If yes), which questions were they?

2. Was the time it took to answer all the questions too long, just right or too short?
   ☐ Too short → How long would you have liked the questionnaire to be? __ __ minutes
   ☐ Just right
   ☐ Too long → How long would you have liked the questionnaire to be? __ __ minutes

   Which items would you remove?

3. Did you find any of the questions upsetting? ☐ No ☐ Yes
   (If yes), which questions were they?

   Could you tell me why they were upsetting?

4. Do you think the questionnaire left out any questions that were important to ask?

Thank you for your participation

A Randomized Phase III Study of Bendamustine Plus Rituximab Versus Ibrutinib Plus Rituximab Versus Ibrutinib Alone in Untreated Older Patients with Chronic Lymphocytic Leukemia (CLL)

Health Care Professional Questionnaire

Assessment Period

- ☐ Prior to Treatment (between pre-registration and start of cycle 1)
- ☐ Day 1 of Cycle 6
- ☐ Progression or 2 Years

This form completed by

Physician *(check one)*	☐ Yes	☐ No
Nurse *(check one)*	☐ Yes	☐ No
CRA *(check one)*	☐ Yes	☐ No

Date Completed: *(mm/dd/yyyy)* __ __/__ __/__ __ __ __ Patient Study ID Number: _____

Patient Initials: _____
L F M

Study Number: A041202

HEALTHCARE PROFESSIONAL INFORMATION SHEET
Health Care Professional Completed Questionnaire

You have been given a booklet to complete for this study. The booklet contains some questions about your patients' functional status, cognition, and nutrition.

1. This booklet is to be completed prior to the patient's first treatment, on day 1 of cycle 6, and at progression or 2 years.

2. The booklet contains 6 set of questions:
   I. Form information
   II. Functional status (Karnofsky Performance Status, Timed "Up and Go")
   III. Cognition (Blessed Orientation-Memory-Concentration Test)
   IV. Scoring
   V. Nutrition
   VI. Questions regarding questionnaires

3. This booklet should be completed by a Nurse, CRA or physician.

4. Directions on how to complete each set of questions are written on the top of the page.

5. Please enter the booklet data into Medidata Rave when finished.

Thank you for taking the time to help us.

Healthcare Professional Questionnaire

II. Functional Status

A. Karnofsky Performance Status *(Healthcare professional rated)**

INSTRUCTIONS: Please rate your assessment of patient's Karnofsky Performance Status as of date this form is completed. (Scale is listed below.)

__ __ __ %

%	CRITERIA
100	Normal: no complaints; no evidence of disease.
90	Able to carry on normal activity; only minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, but unable to carry on normal activity or do active work.
60	Requires occasional assistance, but is able to care for most personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization is indicated although death not imminent.
20	Very sick; hospitalization necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead.

* Physician KPS – Karnofsky, D.A. and Burchenal, J.H., 1949

B. Timed "Up and Go"**

INSTRUCTIONS: The timed "Up and Go" measures, in seconds, the time it takes for an individual to stand up from a standard arm chair (approximate seat height of 46 cm [approximately 1.5 ft]), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair, and sit down again. The subject wears his/her regular footwear and uses their customary walking aid (none, cane, walker, etc.) No physical assistance is given. The subject starts with his back against the chair, his arm resting on the chair's arm, and his walking aid in hand. He is instructed that on the word "go", he is to get up and walk at a comfortable and safe pace to a line on the floor 3 meters (approximately 10 feet) away, turn, and return to the chair and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a wrist watch with a second hand or a stop-watch can be used to time the performance.

Time to perform "Up and Go" __ __ . __ seconds

** Timed "Up and Go" – Podsiadio, D. and Richardson, S., 1991

Healthcare Professional Questionnaire

III. Cognition

This section is only completed prior to treatment (between pre-registration and start of cycle 1) and on day 1 of cycle 6

BLESSED ORIENTATION-MEMORY-CONCENTRATION TEST*					
	Patient's Response	**Maximum errors**	**Score**	**Weight**	**Final score**
1. What year is it now? [without looking at a calendar]	__ __ __ __	1	__ __	x 4 =	__ __
2. What month is it now? [without looking at a calendar]	__ __	1	__ __	x 3 =	__ __
Memory Phrase: Repeat this phrase after me: 'John Brown, 42 Market Street, Chicago'					
3. About what time is it? [within 1 hour]	__ __ : __ __ (24-hour clock)	1	__ __	x 3 =	__ __
4. Count backwards 20 to 1.		2	__ __	x 2 =	__ __
5. Say the months in reverse order.		2	__ __	x 2 =	__ __
6. Repeat the Memory Phrase.		5	__ __	x 2 =	__ __
			TOTAL SCORE:		__ __

Scoring: For items 1 to 3, the response is either correct (score 0) or incorrect (score 1). For items 4 to 6, add one point for each error (item 4 and 5 maximum error is 2; for item 6, maximum error is 5); total all scores in "Final Score" column. Data from participants found to have gross cognitive impairment as determined by the Orientation-Memory-Concentration Score ≥11 will be excluded from the analysis. Maximum score = 28.

* Blessed OMC – Katzman, R., et al., 1983; Kawas, C., et al., 1995

IV. Scoring

This question is only applicable to the BOMC-Test in Section III.

1. Did the patient score greater than or equal to 11 on the Blessed Orientation-Memory-Concentration Test?
   - ☐ No
   - ☐ Yes **(If yes, notify the patient's treating physician.)**

This question is only applicable to question #1 in "Section K. Your Feelings" from the Patient Questionnaire.

2. How did the patient answer the question "Do you often feel sad or depressed?" in the Patient Questionnaire *(Section K)*?
   - ☐ No
   - ☐ Yes **(If yes, notify the patient's treating physician.)**

V. Nutrition

Height (*from patient's chart*) __ __ _ cm

Weight (*from patient's chart*) __ __ __ kg

Weight approximately 6 months ago *(from patient's chart or patients self report)* __ __ __ kg

VI. Questions Regarding Questionnaires

A. Were any of the questionnaires in the Geriatric Assessment – Healthcare Professional Questionnaire difficult for you to administer?

☐ Yes ☐ No

If no, please proceed to the next question.
(If yes), please indicate which questionnaire was difficult to administer *(Mark all that apply with an X.)*

☐ Karnofsky Performance Status (KPS) Healthcare Professional Rated
☐ Timed Up and Go
☐ Blessed Orientation-Memory-Concentration Test
☐ Other
If other, specify _____

B. Were any of the questionnaires in the Geriatric Assessment – Patient Questionnaire difficult for the patient to complete?

☐ Yes ☐ No

If no, please proceed to the next question.
(If yes), please indicate which questionnaire(s) was difficult for the patient to complete *(Mark all that apply with an X.)*

☐ Background Information
☐ Daily Activities
☐ Physical Activities
☐ Current Health Rating
☐ Falls
☐ Your Health
☐ Mental Health
☐ Social Activity
☐ Social Support
☐ Spirituality/Religion
☐ Your Feelings

C. Was the patient able to complete "Geriatric Assessment – Patient Questionnaire" on his/her own?

☐ Yes ☐ No

If yes, please proceed to the next question.

(If no), reason not completed on his/her own *(select the primary reason)*

☐ Not literate (does not read or write)
☐ Visual problem
☐ Fatigue
☐ Questions too difficult (above the patient's reading ability)
☐ Other, specify_____

D. Length of time to complete both the Patient and Healthcare Professional Questionnaires

Length of time to complete healthcare professional questionnaire __ __ __ minutes

Length of time to complete patient questionnaire __ __ __ minutes

Total length of time to complete both questionnaires __ __ __ minutes

Completed by _____ Date form completed __ __ / __ __ / __ __ __ __
(Last name, First name) *M M D D Y Y Y Y*

APPENDIX VI CHILD-PUGH SCORE

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

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

Source:

1. Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964. pp. 50-64.
   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.