

Protocol

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

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This supplement contains the following items:

Original Protocol, final protocol, summary of all amendments.

The statistical analysis plan can be found in the protocol and has not changed during the study.

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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)

An Alliance trial conducted by CALGB, NCCTG, and ACOSOG*

**Lead group*

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, Alliance A041202-PP1, and Alliance A041202-EL1

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

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

The following cooperative groups have formally endorsed this trial. Institutions from these groups must enroll patients and submit data via the CTSU.

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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)

Schema (page 1 of 1)

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 4.8](#))
- 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

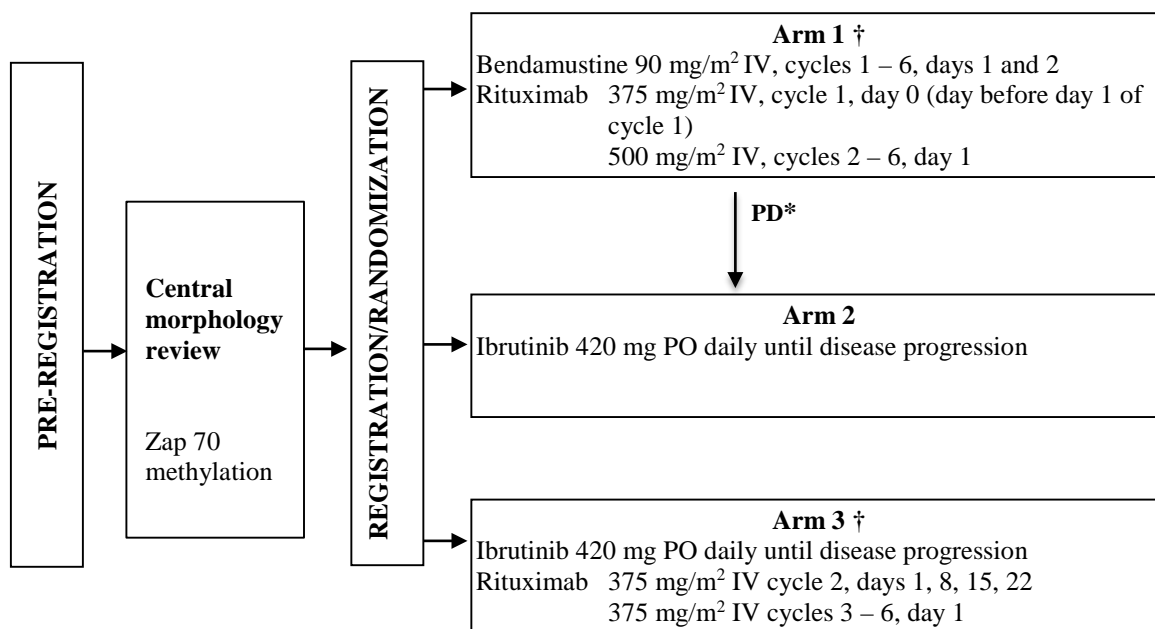
ANC	≥ 1,000/ μ L *
AST and ALT	≤2.5 x ULN **
Total bilirubin	≤1.5 x ULN ***
Creatinine Clearance	≥ 40 mL/min §
Platelet count	≥ 30,000/ μ L

* 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 4.16](#)).



* 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.

† One cycle is 28 days.

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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- κ B. 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 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- κ B,[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.

1.7 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 *CIQA* 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 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.

4.1 Documentation of Disease:

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

- $\geq 5 \times 10^9$ B lymphocytes (5000/ μ L) 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 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 fulfilling criteria for intermediate risk disease plus disease-related anemia (hemoglobin <11 g/dL) or thrombocytopenia (platelet count <100 x 10⁹/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

4.3 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.

4.4 Age ≥ 65 years

4.5 ECOG Performance Status 0-2

4.6 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.

4.7 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.

4.8 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 HIV are eligible if their CD4 count is ≥ 350 cells/mm³ and if they are not taking prohibited CYP-interacting medications (See [Section 4.12](#)).

4.9 Richter's transformation or polymphocytic leukemia

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

4.10 Prednisone or equivalent corticosteroid

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

4.11 Intravenous antibiotics

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

4.12 CYP3A4/5 inhibitor or inducer

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

4.13 Allergy to mannitol

Patients must not have a known allergy to mannitol.

4.14 Significant hypersensitivity to rituximab

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

4.15 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.

4.16 Initial laboratory values

Patients must meet the following required initial laboratory values:

ANC	$\geq 1,000/\mu\text{L}$ unless due to bone marrow involvement
AST or ALT	$\leq 2.5 \times$ upper limits of normal except if due to disease infiltration of the liver
Bilirubin	$\leq 1.5 \times$ upper limits of normal (unless due to liver involvement, hemolysis, or Gilbert's disease)
Creatinine Clearance	≥ 40 mL/min*
Platelet count (untransfused)	$\geq 30,000/\mu\text{L}$

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

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

5.0 REGISTRATION/RANDOMIZATION, STRATIFICATION

5.1 Pre-registration Requirements

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 Central Morphology Review and Zap-70 Methylation

All patients are REQUIRED to be pre-registered to A041202 in order to undergo Zap-70 methylation centrally prior to registration (see [Section 6.2.2](#)). 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 patient enrollment form. Patients must register to A041202 within 14 days of pre-registration.

Patients who consent to CALGB 9665 must pre-register at the time of A041202 pre-registration.

5.2 Registration Requirements

5.2.1 Registration must occur within 14 days of pre-registration and prior to the initiation of therapy.

5.2.2 Registration to the required laboratory correlative science, optional pharmacogenetic, and optional geriatric functional status assessment correlative studies will be performed at the time registration occurs to the treatment study. See [Section 5.4](#) for correlative science registration procedures.

5.3 OPEN Access Requirements

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

All institutions will use OPEN (Oncology Patient Enrollment Network) to enroll patients to this study. OPEN is a web-based registration system for patient enrollment onto NCI-sponsored cooperative group clinical trials. OPEN provides the ability to enroll patients 24 hours a day, 7 days a week.

OPEN may be accessed at <https://open.ctsuo.org>, from the OPEN tab on the CTSU members' website at <https://www.ctsuo.org>, or from the OPEN Registration tab on the Alliance website.

To enroll a patient within OPEN, institution staff must have both of the following:

- A valid and active CTEP-IAM account
- A 'Registrar' role in the Alliance roster or on a participating cooperative group roster

Assignment of the Alliance "Registrar" role is managed through the Alliance Central Protocol Operations Program 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 registration and treatment information. Please print the confirmation for your records.

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

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](#))
- Evaluation of Candidate Pharmacogenetic Determinants of Ibrutinib or Ibrutinib/Rituximab Response (A041202-PP1, [Section 10.3](#))

5.4.2 Registration to Companion Protocol

There is one optional separate companion protocol associated with Alliance A041202, CALGB 9665: The CALGB Leukemia Tissue Bank. This companion protocol **must be offered to all patients** from Alliance sites enrolled on Alliance A041202 (although patients may opt to not participate). This companion protocol requires separate IRB approval. Patients who consent to A041202 and CALGB 9665 must be pre-registered to both studies.

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 6.4](#)), 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 \geq 20% methylation of CpG 3 on Zap-70. Therefore, all patients enrolled on A041202 must have specimens collected at screening to be sent to OSU as outlined in [Sections 6.2](#) and [10.1.3](#). Rai stage at screening, as well as status of del(11q22.3) and del(17p13.1) by FISH, must be documented on enrollment form. Requirements for FISH submission can be found in [Section 6.2.2](#). The primary physician/institutional contact will be notified within 10 days of the Zap-70 results, which must also be documented on the enrollment form. After patient registration, the institutional contact will receive a registration confirmation and treatment confirmation, which includes the randomization arm.

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 14 days of progression documentation. In addition, please make sure to reassess eligibility ([Section 4.0](#)) at re-registration.

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 ctscontact@westat.com.

6.0 DATA AND SAMPLE SUBMISSION

6.1 Data Submission

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS. To access iMedidata/Rave the site user must have an active CTEP IAM account (<https://eapps-ctep.nci.nih.gov/iam>). In addition, Alliance site users must have a role as CRA, Lead CRA, Secondary CRA, Surgical CRA, or Oncology Nurse in the Alliance roster, or an explicit Rave role (Rave CRA, Read-Only, Site Investigator) in RSS at the enrolling site. Non-Alliance site users must have the Rave roles on the CTSU roster at the enrolling sites. The Site Administrator or Data Administrator at the enrolling site may assign the appropriate roles from the Site Roles tab on the CTSU website.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent 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 listed in the upper right pane of the iMedidata screen.

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

6.1.1 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.

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 Submission

6.2.1 Specimen Registration and Tracking

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.

6.2.2 Central Morphology Review and Data Submission for Stratification

All patients must have FISH for del(17p13.1) and del(11q22.3) performed 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 [Sections 6.2.4](#) and [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.

- 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 6.2.1](#) 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, cytochemistry results, and FAB classification.

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

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, Alliance A041202-PP1 and CALGB 9665

Specimen	Baseline	Day 1, Cycle 1	Day 1, Cycle 2*	Day 1, Cycle 9	Month 24**	Remission	Progression	Ship to:
For ALL patients registered to A041202, submit the following (for required correlative study A041202-LC1):								
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 citrate tubes, 1x 5 mL heparin tube, 1 x 5 mL EDTA tube		4x10 mL citrate tubes	4x10 mL citrate tubes	4x10 mL citrate tubes		4x10 mL citrate 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 tube							OSU

* 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.

A Collect and submit only from patients who consent to CALGB 9665.

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

6.2.4.1 Bone Marrow Submission (Alliance A041202-LC1)

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 6.2.1](#).

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
calgb.ltb@osumc.edu

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)

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 6.2.4](#).

Specimens for patients registered on this study must be logged and shipped using the online Alliance BioMS, as described in [Section 6.2.1](#).

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
calgb.ltb@osumc.edu

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)

One buccal cell sample should be obtained from each patient at baseline. As noted in [Section 6.2.4](#), patients who consent to CALGB 9665 will have an additional sample collected on cycle 1 day 1. Have patient rinse mouth with 10mL of mouth wash (e.g. Scope) for 30 to 60 seconds, and then spitting 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. Store the sample at room temperature (do NOT refrigerate, freeze or expose to extreme heat). 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. 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 6.2.1](#).

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
calgb.ltb@osumc.edu

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 Whole Blood Submission (Alliance A041202-PP1)

The whole blood specimen is collected for the correlative study A041202-PP1, described in [Section 10.3](#). From patients who consent to model consent question #2, collect 5 mL 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 6.2.1](#).

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 Biorepository at Ohio State University (OSU):

Alliance Biorepository at Ohio State University
Department of Pathology
Polaris Innovation Centre
2001 Polaris Parkway
Columbus, OH 43240
Tel: 614-293-7073

Fax: 614-293-7967
path.calgb@osumc.edu

Ship specimens on a cold pack by overnight courier to the Alliance Biorepository at OSU 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 (+/- 28 days)		
		Prior to treatment*	End 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. Dr. Arti Hurria or a trained member of her research team will conduct the training. Please call 626-256-4673, x 62507 or email ahurria@coh.org to schedule a time to conduct the geriatric assessment study training with the designated nurse, CRA, or physician.

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)

To be completed within 21 DAYS before registration:

- Bone marrow biopsy
- CT scans

To be completed within 14 DAYS before registration:

- All blood work except FISH analysis
- History and physical

Tests & Observations ¹	Prior To Study	Cycle 1 Day 1	Day 1 of Cycles 2, 3, 5, 6	Day 1 of Cycle 4	Day 1 of Cycle 9	Post-treatment follow-up	24 month follow-up ²	Relapse/ Disease progression
History & progress notes ³	X		X	X	X	A	X	X
Physical examination ³	X		X	X	X	A	X	X
Height ³	X							
Weight / body surface area ^{3,4}	X		X	X	X	A		
Performance status	X		X	X	X	A	X	X
Solicited baseline abnormalities/AEs	X		X	X	X	A	X	
Registration fatigue/uniscale assessment	B							
Laboratory Studies								
FISH for del(11q22.3) and del(17p13.1) (performed locally) ³	X							
Zap-70 methylation (central analysis) ^{3,5}	X							
Complete blood count (CBC)	X	X	X	X	X	A	X	X
Serum creatinine, CrCl (est.), BUN	X	X	X	X	X	A	X	
Serum electrolytes	X	X	X	X	X	A	X	
Uric acid / glucose / phosphate / Ca ⁺⁺	X							
AST, ALT, alk. phos., bilirubin	X		X	X	X	A	X	
LDH, albumin	X		X	X	X	A	X	
Beta-2-microglobulin	X							
Direct antiglobulin test (Coomb's test)	X							
Serum or urine HCG	X							
HBsAg, HBsAb, Hep C, HB core antibody ⁶	X							
Flow cytometry ³	X			X	X		X	X
Serum immunoglobulin	X			X	X	C	X	
Staging								
CT scan (chest, neck, abdomen, & pelvis) ^{1,3}	X			X	X		X	X
Bone marrow asp. & biopsy ^{1,3,7}	D				X		X	X
Additional Required Correlative Samples⁸								
Peripheral whole blood	X		E		X		X	X
Buccal cell sample	X							

- 1 Laboratory studies must be completed on day 1 of specified cycles. CT scans and bone marrow biopsy may be completed up to 7 days prior to specified cycle
- 2 For Arms 2 and 3, only for patients in continued remission; for Arm 1 patients who have crossed over to ibrutinib therapy, 24-month follow-up only for patients who have not experienced a second disease progression.
- 3 Reports and clinic notes must be submitted in PDF form via Medidata Rave.
- 4 The dose of chemotherapy need not be changed unless the calculated dose changes by $\geq 10\%$.
- 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 as well as the randomization arm. See [Section 6.2.2.](#)
- 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](#), [6.2.4](#), 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 consent to participate in the optional companion study CALGB 9665. Please see Sections [5.4](#), [6.2.4](#), [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.
 - A These studies should be performed at least every 3 months for patients on Arms 2 and 3. Ongoing solicited adverse event forms are only necessary for patients still on ibrutinib (Arms 2 and 3). Perform these studies at least every 6 months for patients on Arm 1 who have not crossed over to Arm 2.
 - B To be completed after registration and ≤ 21 days prior to treatment, see [Section 1.7](#) and [Appendix III](#).
 - C Serum immunoglobulin should be performed yearly during follow-up for patients on continuous ibrutinib.
 - D Within 21 days prior to registration, 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 Biorepository at Ohio State University immediately via overnight courier. See [Section 6.2.2.](#)
 - E Day 1 of cycle 2 only, as well as Arm 2 and Arm 3 only.

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.

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/m² IV, then at 500 mg/m² IV on day 1 of cycles 2-6. Bendamustine is given at 90 mg/m² IV on days 1 and 2 of each cycle.

- **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, and bendamustine should be administered prior to rituximab on days that they are both given.
- **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 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 plus rituximab 375 mg/m² 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. 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 <20x10¹²/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 \leq 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 \leq 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.
- Patients who require the initiation of systemic anticoagulation should have ibrutinib held for up to 28 days or until stable on low molecular weight heparin. Concomitant warfarin therapy is prohibited.
- 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., $\geq 50\%$ 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/m ²
-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 \leq 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.
- Patients who require the initiation of systemic anticoagulation should have ibrutinib held for up to 28 days or until stable on anticoagulation. Concomitant warfarin therapy is prohibited.
- 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., $\geq 50\%$ 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., $> 400,000/\text{mcL}$) 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 ($>400,000/\text{mcL}$) 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 \leq 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.

- For infusion reactions attributable to rituximab, supportive care should be provided per institutional protocols. Rituximab can be continued without dose reduction.
- 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.
- For grade 3 or 4 non-hematologic toxicity at least possibly, probably, or definitely attributable to ibrutinib, hold ibrutinib until toxicity returns to \leq 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.

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 OSU. 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 OSU will perform FISH and cytogenetic studies.

Zap-70 methylation will be performed by pyrosequencing at OSU. 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.

DNA mutational analysis will be performed at OSU 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. 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 OSU 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 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 citrate tubes, 1x 5 mL heparin tube, 1 x 5 mL EDTA tube

Bone marrow: 1 x 10 mL EDTA tube

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

Peripheral Blood: 4x10 mL citrate tubes

Day 1 Cycle 9

Peripheral Blood: 4x10 mL citrate tubes

Bone marrow: 1x10mL EDTA tube

24 months

Peripheral Blood: 4x10 mL citrate tubes

Bone marrow: 1x10 mL EDTA tube

Time of Relapse/Progression

Peripheral blood: 4x10 mL citrate 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), the end 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]

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 *CIQA* SNP (rs172378), shown to predict rituximab response in FL, but never tested in CLL[44, 45]

CIQA 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

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 Biorepository at Ohio State University (OSU) for processing. Blood samples will be processed into plasma, PBL and DNA. DNA quality will be assessed by UV spectrophotometry and by agarose gel electrophoresis. All DNA samples will be stored at OSU until they are distributed to the appropriate laboratory for genotyping. For *FCGR3A* and *CIQA* 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 $\geq 10\%$.

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.

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

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (<https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jsp>). Access to OAOP requires the establishment of a CTEP Identify and Access Management (IAM) account (<https://eapps-ctep.nci.nih.gov/iam/>) and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call (240)276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov.

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 (C_{max} and AUC_{0-last}) of ibrutinib by 29- and 24-fold, respectively. Therefore, concomitant administration of ibrutinib with strong inhibitors of CYP3A4/5 (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., $\geq 50\%$ 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.
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, 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, for at least 7 days after the urgent surgical procedure.

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 on physical exam (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 $\geq 1,500/\mu\text{L}$, 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 $\geq 1,500/\mu\text{L}$, 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.

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

- Polymorphonuclear leukocytes $\geq 1,500/\mu\text{L}$ 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

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:

- $\geq 50\%$ 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

- $\geq 50\%$ 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 $\geq 56\%$ 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 $< 100,000/\mu\text{L}$, 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., $\geq 50\%$ 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., $> 400,000/\text{mcL}$) 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. 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 until second disease progression. Upon completing 6 cycles of treatment, Arm 1 patients will be followed at least every 3 months until progression.

Arm 2: Continue treatment until disease progression.

Arm 3: Continue rituximab until cycle 6, then continue ibrutinib until disease progression.

14.1.2 Disease Progression: Remove from protocol therapy any patient with rapid disease progression.

14.1.3 Follow Up Schedule

Patients who end treatment for reasons other than progression and subsequent treatment will go to clinical follow up, followed every 3 months for up to 10 years. Patients who progress or receive a subsequent treatment will go to survival follow up, followed every 6 months for 10 years. Patients who withdraw prior to starting any protocol treatment (with or without progression) will be followed every 6 months for up to 10 years in observation.

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. 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-based 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 H_0	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 $\alpha=0.001$ for gene expression and $\alpha=0.005$ 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. $\alpha=0.001$) and 5 false positive per 1000 features with miRNA data (i.e.

setting $\alpha=0.005$). 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 (H_0 : 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 $\pi_D = p_0 * 0.47 + p_0 * D * 0.53$ where p_0 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					
Ethnic Category	Sex/Gender				
	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 NCI Adverse Event Expedited Reporting System (AdEERS). The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for reporting. All treatment areas should have access to a copy of the CTCAE version 4.0. A copy can be downloaded from the CTEP website (<http://ctep.cancer.gov>).

The Alliance requires investigators to route all expedited adverse event reports through the Alliance Central Protocol Operations Program Office for Alliance-coordinated studies.

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 AdEERS 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 Treatment¹

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 AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

¹Serious 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 AdEERS Expedited Reporting Requirements for Phase 3 Trials Utilizing an Agent Under an IND:

- All adverse events reported via AdEERS (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.
- Deaths clearly due to progressive disease do not require AdEERS, but must be reported as part of study results via routine reporting.
- 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 ASAE 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 new malignancies must be reported through AdEERS 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 4.0, 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 AdEERS 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 28 days after completion of treatment on A041202 must be reported via AdEERS. Use the event term “pregnancy, puerperium, or perinatal condition-other, fetal exposure (grade 4).”
 - AdEERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities).
 - The AdEERS report should be amended for any neonatal deaths or complications occurring within 28 days of birth independent of attribution. Infant deaths occurring after 28 days considered to be related to in utero exposure to the agents used in this trial should be reported via AdEERS.
- 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 Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS

(except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 392 patients.* Below is the CAEPR for PCI-32765 (ibrutinib).

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

Version 2.2, February 28, 2013¹

Adverse Events with Possible Relationship to PCI-32765 (ibrutinib) (CTCAE 4.0 Term) [n= 392]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		<i>Anemia (Gr 2)</i>
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea			<i>Diarrhea (Gr 2)</i>
	Dry mouth		
	Dyspepsia		
	Flatulence		
	Mucositis oral		
	Nausea		<i>Nausea (Gr 2)</i>
	Vomiting		<i>Vomiting (Gr 2)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
	Fatigue		<i>Fatigue (Gr 2)</i>
	Fever		
INFECTIONS AND INFESTATIONS			
	Infection ²		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		
INVESTIGATIONS			
	Neutrophil count decreased		
	Platelet count decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyperuricemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
	Myalgia		

NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		
	Purpura		
	Rash maculo-papular		Rash maculo-papular (Gr 2)

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Hemolysis; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Atrioventricular block first degree; Cardiac disorders - Other (bundle branch block left); Cardiac disorders - Other (extrasystoles); Heart failure; Sinus bradycardia
EAR AND LABYRINTH DISORDERS - Ear pain
EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Eye disorders - Other (eye discharge); Eye disorders - Other (macular edema); Eye disorders - Other (ocular hyperemia); Eye disorders - Other (retinal hemorrhage); Eye disorders - Other (visual acuity reduced); Eye pain; Floaters; Glaucoma; Keratitis; Photophobia; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Colitis; Enterocolitis; Esophagitis; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gingival edema); Gastrointestinal disorders - Other (hypoesthesia oral); Gastrointestinal disorders - Other (irritable bowel syndrome); Gastrointestinal disorders - Other (tongue discoloration); Gastrointestinal hemorrhage³; Oral dysesthesia; Oral pain; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (early satiety); General disorders and administration site conditions - Other (sensation of foreign body); General disorders and administration site conditions - Other (temperature intolerance); Infusion related reaction; Injection site reaction; Malaise; Non-cardiac chest pain; Pain
IMMUNE SYSTEM DISORDERS - Allergic reaction
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (excoriation)
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (blood urea increased); Investigations - Other (cardiac murmur); Investigations - Other (pancytopenia); Lymphocyte count decreased; Weight gain; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (cachexia); Metabolism and nutrition disorders - Other (fluid retention); Metabolism and nutrition disorders - Other (hyperphosphatemia); Metabolism and nutrition

disorders - Other (hypoproteinemia); Metabolism and nutrition disorders - Other (lactose intolerance); Tumor lysis syndrome

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

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

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

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

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

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

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

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

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

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

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.

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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 up to 6 hours after the time it would have been taken. If it is later than 6 hours, the dose should be skipped and the capsules should be taken at the same time as usual the next day.
6. Please return this form 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.

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										As good as
it can be										it can be

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.

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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CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@cts.cocccg.org rg (for submitting regulatory documents only)	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 ctscontact@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 <u>not</u> submit study data or forms to CTSU Data Operations. Do <u>not</u> 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.		
<u>For clinical questions (i.e. patient eligibility or treatment-related)</u> contact the Alliance Study Chair.		
<u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctscontact@westat.com . All calls and correspondence will be triaged to the appropriate CTSU representative.		
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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)

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

* Unless due to bone marrow involvement

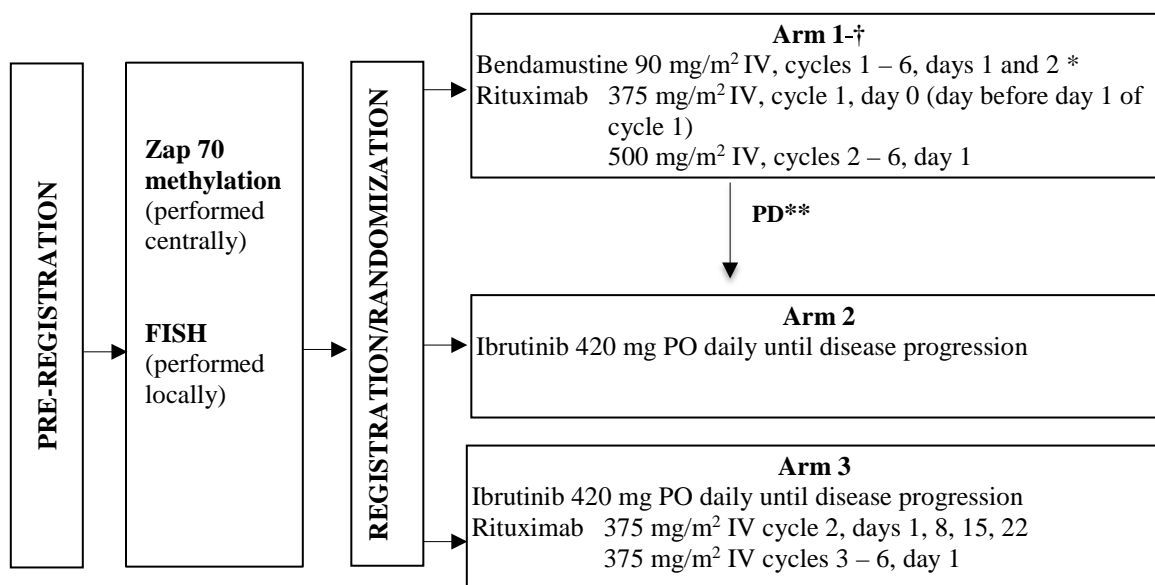
** Except if due to disease infiltration of the liver

*** 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/m².

** 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.

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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- κ B. 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/ μ L) may confer increased risk.

Lymphocytosis

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

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

Atrial Fibrillation

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

Cytopenias

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

Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe.

Infections

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

Second Primary Malignancies

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

Rash

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

Tumor Lysis Syndrome

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

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- κ B,[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 *CIQA* 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:

- $\geq 5 \times 10^9$ B lymphocytes ($5000/\mu\text{L}$) 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 x $10^9/\text{L}$) 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	$\geq 1,000/\mu\text{L}$ unless due to bone marrow involvement
AST or ALT	$\leq 2.5 \times$ upper limits of normal except if due to disease infiltration of the liver
Bilirubin	$\leq 1.5 \times$ upper limits of normal (unless due to liver involvement, hemolysis, or Gilbert's disease)
Creatinine Clearance	≥ 40 mL/min*
Platelet count (untransfused)	$\geq 30,000/\mu\text{L}$

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

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

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 Investigator Registration Procedures

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

Registration requires the submission of:

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

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

5.3.2 CTEP Associate Registration Procedures

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

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

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

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

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

5.3.3 CTSU Registration Procedures

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

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at <https://www.ctsus.org>. For sites under the CIRB initiative, IRB data will automatically load to RSS.

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.ctsus.org> and log in to the members' area using your CTEP-IAM username and password

Click on the Protocols tab in the upper left of your screen

Click on the NCTN Alliance link to expand, then select trial protocol A041202.

Click on the Site Registration Documents link.

Requirements for A041202 Site Registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.cocccg.org (for regulatory document submission only)

Checking Your Site's Registration Status:

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

Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password

Click on the Regulatory tab at the top of your screen

Click on the Site Registration tab

Enter your 5-character CTEP Institution Code and click on Go

5.3.4 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 $\geq 20\%$ 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 5×10^9 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 ctscontact@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 Studies¹						
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	X		X
Serum electrolytes	X	X	X	X		X
Uric acid / glucose / phosphate / Ca ⁺⁺	X					X
AST, ALT, PT INR, alk. phos., bilirubin	X		X	X		X
LDH, albumin	X		X	X		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 Samples⁸						
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 1 and 2, 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 $\geq 10\%$.
- 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 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 \leq 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/m² IV, then at 500 mg/m² IV on day 1 of cycles 2-6. Bendamustine is given at 90 mg/m² 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/m² rather than 90. Subsequent cycles should be administered at 90 mg/m².

- **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/m² 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	$\geq 75\%$	< 500

*Platelet counts must be below normal levels for any grade toxicity to be recorded. If platelet count is $< 20 \times 10^{12}/L$, 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 \leq 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 \leq 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., $\geq 50\%$ 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., $> 400,000/\text{mcL}$) 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 ($>400,000/\text{mcL}$) 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/m ²
-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 \leq 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., $\geq 50\%$ 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., $> 400,000/\text{mcL}$) 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 ($>400,000/\text{mcL}$) 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/m²	420 mg
-1	50 mg/m²	280 mg
-2	30 mg/m²	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 \leq 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 \leq 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 *CIQA* SNP (rs172378), shown to predict rituximab response in FL, but never tested in CLL[44, 45] *CIQA* 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 *CIQA* 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 $\geq 10\%$.

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

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (<https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jsp>). Access to OAOP requires the establishment of a CTEP Identify and Access Management (IAM) account (<https://eapps-ctep.nci.nih.gov/iam/>) and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call (240)276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov .

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 (C_{max} and AUC_{0-last}) of ibrutinib by 29- and 24-fold, respectively. Therefore, concomitant administration of ibrutinib with strong inhibitors of CYP3A4/5 (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., $\geq 50\%$ 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 on physical exam (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 $\geq 1,500/\mu\text{L}$, platelets $> 100,000/\mu\text{L}$, hemoglobin > 11.0 g/dL (untransfused); lymphocyte count $< 5,000/\mu\text{L}$;
- 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 $< 1,500/\mu\text{L}$, platelets $< 100,000/\mu\text{L}$) 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 $\geq 1,500/\mu\text{L}$, platelets $> 100,000/\mu\text{L}$) 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 $\geq 50\%$ decrease in peripheral lymphocyte count from pre-treatment value, $\geq 50\%$ reduction in lymphadenopathy of as many as 6 measurable lymph nodes, and/or $\geq 50\%$ reduction in splenomegaly/hepatomegaly for a period of at least two months. Additionally, these patients must have one of the following:

- Polymorphonuclear leukocytes $\geq 1,500/\mu\text{L}$ or 50% improvement from pre-treatment value
- Platelets $> 100,000/\mu\text{L}$ or 50% improvement from pre-treatment value
- Hemoglobin $> 11.0 \text{ g/dL}$ (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 $\geq 50\%$.

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)
- $\geq 50\%$ increase in the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one lymph node must be $\geq 2 \text{ cm}$), appearance of new palpable lymph nodes
- $\geq 50\%$ 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 $\geq 56\%$ prolymphocytes)
- The progression of any cytopenia defines disease progression (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels $>2 \text{ g/dL}$ or to $< 10 \text{ g/dL}$, or by a decrease of platelet counts $> 50\%$ or to $< 100,000/\mu\text{L}$, 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., $\geq 50\%$ 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., $> 400,000/\text{mcL}$) 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 ibrutinib 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-based 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 $\alpha=0.001$ for gene expression and $\alpha=0.005$ 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. $\alpha=0.001$) and 5 false positive per 1000 features with miRNA data (i.e. setting $\alpha=0.005$). 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 (H_0 : 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 $\pi_D = p_0 * 0.47 + p_0 * D * 0.53$ where p_0 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					
Ethnic Category	Sex/Gender				
	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 Treatment¹

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.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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.

¹Serious 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 ASAE 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, 2018¹

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

Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 5.0 Term) [n= 2082]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Fever		
		Sudden death NOS	
HEPATOBIILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
	Infection ³		<i>Infection³ (Gr 3)</i>
		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			<i>Neutrophil count decreased (Gr 4)</i>
	Platelet count decreased		<i>Platelet count decreased (Gr 4)</i>
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
		Hyperuricemia	
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Muscle cramp		
	Myalgia		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (benign neoplasm of skin) ⁵		
		Treatment related secondary malignancy ⁵	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		
		Peripheral sensory neuropathy	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		<i>Cough (Gr 2)</i>
	Dyspnea		
		Pneumonitis ⁶	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			

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%)	
		Skin and subcutaneous tissue disorders - Other (angioedema) ⁷	
	Skin and subcutaneous tissue disorders - Other (rash) ⁸		<i>Skin and subcutaneous tissue disorders - Other (rash)⁸ (Gr 3)</i>
		Stevens-Johnson syndrome	
VASCULAR DISORDERS			
	Hypertension		
		Hypotension	
	Vascular disorders - Other (hemorrhage) ⁹		

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

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

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

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

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

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

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

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

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

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

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

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

EAR AND LABYRINTH DISORDERS - Ear pain

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

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

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

HEPATOBIILIARY DISORDERS - Cholecystitis

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

INFECTIONS AND INFESTATIONS - Conjunctivitis

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

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

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

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

NERVOUS SYSTEM DISORDERS - Depressed level of consciousness; Dysgeusia; Encephalopathy; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (mental impairment); Nervous system disorders - Other (parosmia); Nervous system disorders - Other (PML); Paresthesia; Reversible posterior leukoencephalopathy syndrome; Somnolence; Stroke; Syncope

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

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

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

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

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

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

Note: Ibrutinib (PCI-32765) in combination with other agents could cause an exacerbation of any adverse event

currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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 NCIC 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										As good as
it can be										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

Page 1 of 13

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

Self Assessment Measure – Patient Questionnaire

Page 2 of 13

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).*

- | | |
|--|--|
| <input type="checkbox"/> 8 th grade or less | <input type="checkbox"/> Vocational/technical school |
| <input type="checkbox"/> 9-11 th grade | <input type="checkbox"/> Bachelor's degree |
| <input type="checkbox"/> High school graduate/GED | <input type="checkbox"/> Advanced degree |
| <input type="checkbox"/> Associate degree/some college | <input type="checkbox"/> I prefer not to answer |

2. What is your marital status? *(Mark one with an X.)*

- | | |
|---|---|
| <input type="checkbox"/> Married | <input type="checkbox"/> Separated |
| <input type="checkbox"/> Domestic partnership | <input type="checkbox"/> Never married |
| <input type="checkbox"/> Widowed | <input type="checkbox"/> I prefer not to answer |
| <input type="checkbox"/> Divorced | |

3. With whom do you live? *(Mark all that apply with an X.)*

- | | |
|--|---|
| <input type="checkbox"/> Spouse / partner | <input type="checkbox"/> Parent(s)/ parent(s)-in-law |
| <input type="checkbox"/> Girlfriend / boyfriend | <input type="checkbox"/> Live alone |
| <input type="checkbox"/> Children aged 18 years or younger | <input type="checkbox"/> Other specify _____ |
| <input type="checkbox"/> Children aged 19 years or older | <input type="checkbox"/> Other relative specify _____ |

4. What is your current employment status? *(Mark one with an X.)*

- | | |
|---|--|
| <input type="checkbox"/> Employed 32 hours or more per week | <input type="checkbox"/> Unemployed |
| <input type="checkbox"/> Employed less than 32 hours per week | <input type="checkbox"/> Retired |
| <input type="checkbox"/> Homemaker | <input type="checkbox"/> Full-time student |
| <input type="checkbox"/> Disabled | <input type="checkbox"/> Part-time student |
| <input type="checkbox"/> On medical leave | <input type="checkbox"/> Other specify _____ |

Self Assessment Measure – Patient Questionnaire

Page 3 of 13

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

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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. <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Lifting or carrying groceries	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Climbing <u>several</u> flights of stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. Climbing <u>one</u> flight of stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Bending, kneeling, or stooping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. Walking <u>more than a mile</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Walking <u>several blocks</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. Walking <u>one block</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
j. Bathing or dressing yourself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

Self Assessment Measure – Patient Questionnaire

Page 5 of 13

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? _ _ _

Self Assessment Measure – Patient Questionnaire

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.)

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

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

Self Assessment Measure – Patient Questionnaire

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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

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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.

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

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

Self Assessment Measure – Patient Questionnaire

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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

Self Assessment Measure – Patient Questionnaire

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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.*)

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

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

Self Assessment Measure – Patient Questionnaire

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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

Self Assessment Measure – Patient Questionnaire

Page 12 of 13

K. YOUR FEELINGS*1. Do you often feel sad or depressed? *(Mark one with an X.)*☐ No ☐ Yes2. 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

Self Assessment Measure – Patient Questionnaire

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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 (<i>check one</i>) | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| Nurse (<i>check one</i>) | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
| CRA (<i>check one</i>) | <input type="checkbox"/> Yes | <input type="checkbox"/> 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

Page 1 of 5

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

Page 2 of 5

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

Page 3 of 5

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 <u>year</u> is it now? [without looking at a calendar]	_ _ _ _ _	1	_ _	x 4 =	_ _
2. What <u>month</u> 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 <u>time</u> is it? [within 1 hour]	_ _ : _ _ (24-hour clock)	1	_ _	x 3 =	_ _
4. <u>Count</u> 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. NutritionHeight (*from patient's chart*) __ __ __ cmWeight (*from patient's chart*) __ __ __ kgWeight 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 _____
(Last name, First name)

Date form completed __ __ / __ __ / __ __ __ __
M M D D Y Y Y Y

APPENDIX VI CHILD-PUGH SCORE

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

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

Source:

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

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

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

☒ **Update:**

☒ Eligibility changes

☒ Therapy / Dose Modifications / Study Calendar changes

☒ Informed Consent changes

☒ Scientific / Statistical Considerations changes

☒ Data Submission / Forms changes

☒ Editorial / Administrative changes

☐ Other :

☐ **Status Change:**

☐ Activation

☐ Closure

☐ Suspension / temporary closure

☐ Reactivation

IRB Review of this update is required within 90 days. Full Board review is recommended.

Please follow your local IRB guidelines.

Patient re-consent is required at the next study visit as the A041202-LC1 buccal cell sample was mistakenly omitted from the informed consent document. If a patient does not provide re-consent or is deceased, please alert the protocol coordinator.

UPDATES TO THE PROTOCOL:

References to the “Adverse Event Expedited Reporting System (AdEERS)” have been changed to “CTEP Adverse Event Reporting System (CTEP-AERS)” throughout the protocol.

Cover Page

- In keeping with new CTEP PIO requirements, the following text has been removed from under the study title: “An Alliance trial conducted by CALGB*, NCCTG, and ACOSOG *Lead group.”
- The text “Clinicaltrials.gov identifier: NCT01886872” has been added after the study title.
- The following underlined text has been added after “Optional Companion Studies”: “CALGB 9665 (temporarily suspended on February 28, 2014).”
- The telephone number for Kristy Richards, the Population Pharmacology and Pharmacogenetics Co-Chair, has been corrected from “919-996-0374” to “919-966-0374.”
- The following text has been added to the bottom of the page, “Participating NCTN Groups: Alliance, ECOG/ACRIN, NRG, SWOG and NCIC.”

Cover Page (page 2)

- The Alliance website has been changed from “www.alliance-website.org” to “www.allianceforclinicaltrialsinoncology.org.”
- The Expedited Adverse Event Reporting website has been updated to “https://eapps-ctep.nci.nih.gov/ctepaers/.”
- Under “Protocol Resources,” the e-mail address “calgb.ltb@osumc.edu” has been removed for the Alliance Hematologic Malignancy Biorepository. This change has been made throughout the protocol document.
- Under “Protocol-related questions may be directed as follows:” the contact for questions regarding CTEP-AERS has been changed from “Linda Bressler, PharmD” to the general e-mail address “regulatory@allianceNCTN.org
- A document history table has been added to the bottom of this page.

Cover Page (Page 3)

- As requested by CTEP, the CTSU address and contact information table has been updated.
- As CTEP has discontinued the intergroup endorsement policy, the following text has been removed from under the CTSU Information Table: “The following cooperative groups have formally endorsed this trial. Institutions from these groups must enroll patients and submit data via the CTSU.” The header, “Participating Groups:” has been added in its place.

Schema

- In the schema diagram, “Central Morphology Review” has been removed prior to “Registration/Randomization” to clarify that it will not be used for eligibility screening or randomization.
- In the schema diagram, the following underlined text has been added “Zap 70 methylation (performed centrally).” Additionally, “FISH (performed locally)” has been added to the schema prior to “Registration/Randomization” to clarify that FISH will be used for stratification.

Section 4.0 (Eligibility Criteria)

The following text has been added to the end of the section: “All patient eligibility criteria must be verified prior to registration.”

Section 5.1 (Pre-registration Requirements [Step 0])

“(Step 0)” has been added to the section title for clarity.

Section 5.1.2 (Zap-70 Methylation)

- The underlined text has been removed from the section title, “Central Morphology Review and Zap-70 Methylation.”
- The first sentence has been revised for clarity and now reads as follows: “All patients are REQUIRED to be pre-registered to A041202 in order to submit peripheral blood to OSU for central Zap-70 methylation prior to registration (see [Section 6.2.1](#)).” The sentence previously read: “All patients are REQUIRED to be pre-registered to A041202 in order to undergo Zap-70 methylation centrally prior to registration (see [Section 6.2.1](#)).”
- The second to last sentence has been revised to read: “Results of Zap-70 are needed for patient registration, and patients must register to A041202 within 14 days of notification of Zap-70 results.” The sentence previously read: “Patients must register to A041202 within 14 days of pre-registration.”
- The following text has been added as the last sentence of the section: “Zap-70 results are only used for stratification purposes and DO NOT determine patient eligibility.”

Section 5.1.3

This section has been removed as CALGB 9665 was temporarily suspended to new patient accrual on February 28, 2014.

Section 5.2 (Registration Requirements [Step 1])

“(Step 1)” has been added to the section title for clarity.

Section 5.2.1

- The following text has been added at the beginning of the section, “FISH must be performed locally within 30 days prior to registration (see [Section 6.2.1](#)).”
- In the second sentence, “within 14 days of pre-registration” has been changed to “within 14 days of notification of Zap-70 results.”
- The following text has been added to the end of the section, “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.”

Section 5.2.2

- The specific correlative study names (i.e. A041202-LC1) have been added to the section for clarity.
- The following text has been added as the second sentence, “Patients should not be enrolled on the A041202-EL1 correlative study until institutional staff have been trained (see [Section 5.4.2](#)).”

Section 5.3 (Registration Procedures)

- The title of the section has been changed from “OPEN Access Requirements” to “Registration Procedures.”
- The entire section has been replaced with registration language provided by CTSU and CTEP. Subsections [5.3.1](#), [5.3.2](#), [5.3.3](#) and [5.3.4](#) have been created to organize the section.

Section 5.4.1 (Registration to Correlative Studies Described in Section 10.0)

The following sentence has been added after the second bullet: “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](#).”

Section 5.4.2 (Site Credentialing for Companion Study A041202-EL1)

This section has been added to provide instruction for geriatric assessment training completion. New instructions have also been added for accessing the online training module. Sites should not register patients to A041202 unless this training has been completed. Subsequent sections have been renumbered.

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

- “(Temporarily Suspended as of February 28, 2014)” has been added to the end of the section title.
- The following text has been removed from the section: “This companion protocol must be offered to all patients from Alliance sites enrolled on Alliance A041202 (although patients may opt to not participate). This companion protocol requires separate IRB approval. Patients who consent to A041202 and CALGB 9665 must be pre-registered to both studies.”
- The following text has been added in its place: “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.”

Section 5.5 (Stratification)

- The text “(performed centrally)” has been added to the end of the first sentence of the section.
- The following text has been removed from the section as it now appears in [Sections 5.1.2](#) and [5.2.1](#): “Therefore, all patients enrolled on A041202 must have specimens collected at screening to be sent to OSU as outlined in Sections 6.2 and 10.1.3. Rai stage at screening, as well as status of del(11q22.3) and del(17p13.1) by FISH, must be documented on enrollment form. Requirements for FISH submission can be found in Section 6.2.1. The primary physician/institutional contact will be notified within 10 days of the Zap-70 results, which must also be documented on the enrollment form. After patient registration, the institutional contact will receive a registration confirmation and treatment confirmation, which includes the randomization arm.”

Section 6.1 (Data Submission)

The text in this section has been updated to reflect the new language provided by CTEP and CTSU.

Section 6.2 (Specimen Submission)

This section now includes the body text that previously appeared under [Section 6.2.1](#) (formerly titled “Specimen Registration and Tracking”).

Section 6.2.1 (Specimen and Data Submission for Stratification)

The section title has been changed from “Specimen Registration and Tracking” to “Specimen and Data Submission for Stratification.” Additionally, the first two paragraphs that previously appeared under [Section 6.2.2](#) have been moved to this section.

Section 6.2.2 (Central Morphology Review)

The underlined text has been removed from the section title, “Central Morphology Review and Data Submission for Stratification.”

Section 6.2.2.4

In the last sentence of the second to last paragraph of the section, “FAB classification” has been removed as it is not applicable to CLL. The sentence previously read: “These reports must include differential cell counts, cytochemistry results, and FAB classification.”

Section 6.2.3 (Specimen Submission for Correlative Protocol: CALGB 9665)

The following text has been added to the beginning of the section: “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.”

Section 6.2.4. (Specimen Submission for Correlative Studies Alliance A041202-LC1, Alliance A041202-PP1 and CALGB 9665)

- Footnote “*” has been added after the “Baseline” column title. Below the table, the footnote reads: “Baseline samples may be sent at any point from the date of pre-registration, but must be sent prior to the initiation of therapy.” Subsequent footnotes have been renamed.
- Footnote “***” has been added after “Day 1, Cycle 9.” Below the table, the footnote reads: “Day 1 of Cycle 9 should fall 84 days (+/- 7) after Day 1 of Cycle 6.” Subsequent footnotes have been renamed.
- The following text has been added at the beginning of Footnote “*****” underneath the table: “Month 24 specimens should be collected and submitted approximately 730 days (+/- 10) from Day 1 of Cycle 1.”
- Under “For ALL patients registered to A041202...,” in the “peripheral whole blood” row and “baseline” column, footnote “§” has been added after “1 x 5 mL EDTA tube.” Below the table, the footnote reads: “EDTA tube must be submitted at pre-registration (for Zap-70 Methylation).”
- References to “citrate tubes” have been changed to “acid citrate dextrose (ACD) tubes” or “ACD tubes” throughout the table. This clarification has also been made throughout the protocol document.
- The shipping destination for the peripheral whole blood sample for the A041202-PP1 correlative has been changed from the Biorepository at Ohio State University (OSU) to the Alliance Hematologic Malignancy Biorepository (HEME). This change has been made throughout the protocol document.
- In the last row of the specimen submission table, a 1 mL bone marrow aspirate specimen has been added for the A041202-PP1 correlative.
- Footnote “A” has been modified to read: “Collect and submit only from patients who enrolled on CALGB 9665 prior to the temporary suspension on February 28, 2014.” The footnote previously read: “Collect and submit only from patients who consent to CALGB 9665.”

Section 6.2.4.3 (Buccal Cell Sample Submission [Alliance A041202-LC1])

- In the second sentence of the first paragraph, the text “As noted in Section 6.2.4, patients who consent to CALGB 9665 will have an...” has been changed to “As noted in Section 6.2.4, patients who enrolled on CALGB 9665 prior to February 28, 2014 will have an...”
- In the first paragraph, the following text has been added after the second sentence: “**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....”
- The following sentence was removed from the first paragraph, “Store the sample at room temperature (do NOT refrigerate, freeze or expose to extreme heat),” and replaced with the following text: “Keep any samples refrigerated until you are ready to ship.”
- The following sentence has been added towards the end of the paragraph: “Buccal cell samples for A041202-LC1 and CALGB 9665 should not be collected on the same day.”

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

- The following underlined text has been added to the section title, “Bone Marrow Aspirate and Whole Blood Submission (Alliance A041202-PP1).”
- In the first paragraph, the following text has been added to the beginning of the first sentence: “One mL of the initial bone marrow aspirate and....”
- The second sentence of the first paragraph has been revised to read: “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.” The sentence previously read: “From patients who consent to model consent question #2, collect 5 mL of whole blood in an EDTA tube at baseline.”

- In the third and fourth paragraphs, the shipping location and address have been changed from the Alliance Biorepository at OSU to the Alliance Hematologic Malignancy Biorepository (HEME).

Section 6.3 (Geriatric Assessment [Alliance A041202-EL1])

- In the first paragraph below the table, “(See [Section 5.4.2](#))” has been added to the end of the first sentence. Additionally, the following two sentences have been removed as the training can be conducted via an online module: “Dr. Arti Hurria or a trained member of her research team will conduct the training. Please call 626-256-4673, x 62507 or email ahurria@coh.org to schedule a time to conduct the geriatric assessment study training with the designated nurse, CRA, or physician.” Instructions for accessing the online Geriatric Assessment training module appear in [Section 5.4.2](#):
- The following text has been added as the second paragraph below the table: “Geriatric Assessment questionnaire booklets for A041202-EL1 are to be ordered prior to the registration of any patients. Patient completed questionnaires and 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.”

Section 7.0 (Required Data)

- The pre-study testing interval for the bone marrow biopsy and CT scans has been changed from “21 DAYS before registration” to “28 DAYS before registration.”
- The “Day 1 of Cycle 9” column has been removed, and the studies previously listed under “Day 1 of Cycle 9” are now included under the “Post- treatment follow up” column. Please note that only changes to the table layout have been made, and that no changes have been made to the testing schedule. Due to this merger, the following changes have been made to [Section 7.0](#):
 - The following underlined text has been added to footnote “C:” “Serum immunoglobulin should be performed 84 days (+/-7) after Day 1 of Cycle 6, and then yearly during follow-up for patients on continuous ibrutinib.
 - In the “post treatment follow up” column, footnote “F” has been added to flow cytometry, CT scan, bone marrow asp. & biopsy and peripheral blood. The footnote reads: “For all patients, ONLY perform 84 days (+/- 7) after Day 1 of Cycle 6.” These studies were previously included in the “Day 1 of Cycle 9” column with an “X.”
- The following changes have been made within the study calendar table:
 - The “Flow cytometry” laboratory study has been renamed “Peripheral blood flow cytometry” for clarity.
 - The following underlined text has been added to the laboratory study title for clarity, “Serum immunoglobulins (IgG, IgA, IgM).”
- Footnote “*” has been added after the column header “Post-treatment follow up.” Below the table, the footnote reads: “Post-treatment follow-up applies to all patients (including those patients who have completed treatment on Arm 1, those still continuing to receive ibrutinib and patients who have gone off protocol treatment).”
- Below the table, the following text has been added to the beginning of footnote “2”: “Month 24 follow-up should be completed approximately 730 days (+/- 10) from Day 1 of Cycle 1.”
- Within footnote “5,” the text “as well as the randomization arm” has been removed from the end of the second sentence as the randomization arm will be communicated after patient registration.
- In footnote “8,” the text “...as well as those who consent to participate in the optional companion study CALGB 9665” has been changed to “...as well as those who enrolled on CALGB 9665 prior to the temporary suspension on February 28, 2014.”

- Footnote “9” has been added to “Serum or urine HCG” under “Laboratory Studies” in the study calendar table. The footnote reads: “Only required for women of childbearing potential.”
- In footnote “A,” the first sentence has been modified to require follow-up tests every 84 days (+/- 7) for all patients, not just those on Arms 2 and 3. Additionally, the last sentence has been removed, which previously read as follows: “Perform these studies at least every 6 months for patients on Arm 1 who have not crossed over to Arm 2.”
- In footnote “D,” the testing interval for bone marrow analysis and central morphology review has been changed from “Within 21 days prior to registration” to “Within 28 days prior to registration.”
- Footnote “E” has been revised as follows to avoid confusion: “Submit only on Day 1 of cycle 2 for patients on Arms 2 and 3. See [Section 6.2.4](#).” The footnote previously read: “Day 1 of cycle 2 only, as well as Arm 2 and 3 only.”

Section 8.1 (Arm 1: Bendamustine/Rituximab)

Under the “Drug administration” bullet, text has been modified to read as follows: “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.” The text previously read: “Bendamustine and rituximab are both administered intravenously, and bendamustine should be administered prior to rituximab on days that they are both given.”

Section 8.2 (Arm 2 Ibrutinib)

The following underlined text has been added to the first sentence of the section: “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.”

Section 8.3 (Arm 3 Ibrutinib/Rituximab)

The following underlined text has been added to the first sentence of the section for clarification: “Treatment on this arm consists of ibrutinib 420 mg PO daily, on days 1-28 of each 28-day cycle, plus rituximab....”

Section 9.1.2 (Arm 2)

The second bullet has been revised and moved to [Section 9.2](#). The bullet formerly read: “Patients who require the initiation of systemic anticoagulation should have ibrutinib held for up to 28 days or until stable on anticoagulation. Concomitant warfarin therapy is prohibited.”

Section 9.1.3 (Arm 3)

The second bullet has been revised and moved to [Section 9.2](#). The bullet formerly read: “Patients who require the initiation of systemic anticoagulation should have ibrutinib held for up to 28 days or until stable on anticoagulation. Concomitant warfarin therapy is prohibited.”

Section 9.2 (Dose Adjustments for Non-Hematologic Toxicity)

- The fourth bullet text has been moved and now appears as the second bullet in the section.
- A fifth bullet has been added that reads: “Patients who require the initiation of systemic anticoagulation should have ibrutinib held for at least 5 days and up to 28 days on a stable dose of low molecular weight heparin. Concomitant warfarin therapy is prohibited.” Similar text previously appeared in [Sections 9.1.2](#) and [9.1.3](#).
- A sixth bullet has been added that reads: “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.”

Section 10.1.1 (Background)

- References to OSU in this section have been changed to “Ohio State University” in order to avoid confusion with the Alliance Biorepository at OSU (OSU).
- The following sentence has been added to the end of the third paragraph: “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.”
- The underlined text has been added to the end of the second sentence in the fifth paragraph: “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.”

Section 10.1.2 (Objectives)

The following underlined text has been added to the third bullet: “To determine whether baseline microRNA and gene expression markers in cells or plasma microvesicles are correlated with clinical outcomes....”

Section 10.1.3 (Sample Requirements)

Under “Baseline,” the following text has been added: “Buccal cell sample: 50 mL sterile tube.” The sample appears throughout the protocol but was mistakenly omitted in this section.

Section 10.2.2 (Study Design)

The following sentence has been added to the end of the section: “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](#).”

Section 10.3.3 (Methods)

- The underlined text has been added at the beginning of the section: “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....”
- The following sentence was added as the fifth sentence of the paragraph: “If needed, B-cells can be removed by magnetic bead purification to eliminate CLL cells from the samples.”

Section 11.1 (Rituximab)

Under “Administration,” the following text has been added at the end of the second paragraph: “These guidelines are recommended. Individual institutions may follow institutional guidelines for rituximab administration.”

Section 13.1.2 (Partial Response)

A fourth bullet has been added as follows: “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 $\geq 50\%$.”

Section 15.1 (Overview and Study Design)

The following text has been added as the second sentence in the first paragraph: “This study will not be blinded.”

Appendix I (Patient Medication Diary)

- To be consistent with the protocol, the fifth bullet now reads, “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.” The instructions previously read: “If you miss a dose, it can be taken up to 6 hours after the time it would have been taken. If it is later than 6 hours, the dose should be skipped and the capsules should be taken at the same time as usual the next day.”
- The underlined text has been added to bullet #6, “Please return this form and the bottle with any leftover capsules to your physician when you go for your next appointment.”

Appendix V (Geriatric Assessment [A041202-EL1] Measures)

This appendix has been added to include the patient and healthcare professional questionnaires required for participation in the A041202-EL1 geriatric assessment correlative study. Note that this appendix is for reference and IRB submission only. They are not to be used for patient completion.

UPDATES TO THE MODEL CONSENT:

Why is this study being done?

- The following underlined text has been removed from the fourth sentence: “Both bendamustine and rituximab are approved by the FDA to treat chronic lymphocytic leukemia (your leukemia type), but ibrutinib is considered investigational.” Two sentences have been added in its place, which read: “Ibrutinib is FDA approved for patients who have received previous treatment for CLL. For this study, ibrutinib is considered investigational, since you have never been treated before for CLL.”
- The following sentence has been added to the section: “The combination of the drugs ibrutinib and rituximab (Arm 3) is also considered investigational.”

What will happen if I take part in this study?

- Under “During the study...,” CT scan and bone marrow aspirate and biopsy have been added under this section. These studies were previously included under the heading “You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.”
- The underlined text has been added to the second bullet, “CT scan (chest, neck, abdomen & pelvis) at 3 months, 8 months and 24 months after you start the treatment, and if your disease progresses (gets worse).”
- Under “You will need these tests and procedures that are not part of regular cancer care because you are in this study,” the following has been added as the first bullet:
“A sample of cells from inside your mouth (buccal cell sample) will be taken only once, before you start treatment. For the buccal cell sample, we will ask you to swish a small amount of mouthwash (like Scope) in your mouth for 30-60 seconds, and then spit the mouthwash into a container. This will provide buccal cells, which are not involved with your disease.”
The required sample was already included throughout the protocol, but was mistakenly omitted in the consent document.
- Under “If you are in Arm 1 (often called ‘Group A’),” the third paragraph has been split into two paragraphs. The fourth paragraph now begins with “If you miss a dose of ibrutinib....”
- Under the three treatment sections (“If you are in Arm 1 [often called ‘Group A’],” “If you are in Arm 2 [often called ‘Group B’]...” and “If you are in Arm 3 [often called ‘Group C’]...”) the fourth

paragraphs have been revised as follows, “If you miss a dose of ibrutinib, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. You should not take extra capsules to make up a missed dose...” The instructions in all three sections previously specified a 6 hour window to make up a missed dose of ibrutinib, which was inconsistent with the instructions provided in the protocol.

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

The following language, from the new CTEP model consent, has been added before the bendamustine risk list:

“If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor’s office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The agents used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The table below shows the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.”

Risks and side effects related to Bendamustine:

The risk list for bendamustine has been updated to reflect the NCI’s new condensed risk profile format. The former “Likely” category has been replaced with “Common, Some May Be Serious,” the former “Less Likely” category has been replaced with “Occasional, Some May Be Serious,” and the former “Rare but Serious” has been replaced with “Rare, and Serious.”

- The following changes have been made within “Common, Some May Be Serious” to be consistent with CTEP’s new condensed risk format for bendamustine:
 - “Lowered white blood cell count (neutrophils) that may lead to infection” and “Infection” have been combined and replaced with “Infection, especially when white blood cell count is low.”
 - “Lowered platelets, which may lead to an increase in bruising or bleeding” has been replaced with “Bruising, bleeding.”
 - “Lowered red blood cells, which may cause anemia, tiredness or shortness of breath” is now covered under “Anemia which may cause tiredness, or may require blood transfusions” and “Cough, shortness of breath.”

- “Fatigue” is now covered under “Fever, tiredness.”
- The risks “constipation” and “diarrhea” have been moved to this section from “Occasional, some may be serious.” The risks have been combined to read, “Constipation, diarrhea, nausea, vomiting.”
- “Loss of appetite” has been moved to this section from “Occasional, some may be serious.” The risk now reads, “Weight loss, loss of appetite.”
- “Headache” has been added.
- The following changes have been made within “Occasional, Some May Be Serious” to be consistent with CTEP’s new condensed risk format for bendamustine:
 - “Rash” has been replaced with “Itching, rash.”
 - “Heartburn” and “Irritation or sores in the lining of the throat” have been combined and replaced with “Sores in the mouth or throat which may cause difficulty swallowing and/or heartburn.”
 - “Blood infection” and “pneumonia” have been combined and replaced with “Severe blood infection, pneumonia.”
 - The following risks have been moved to this section from “Rare, and serious:”
 - “Severe side effects during the infusion or shortly after, or severe allergic reactions including shortness of breath, swelling of the throat, and low blood pressure” has been moved and replaced with “Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat.”
 - “Development of a second cancer such as leukemia” has been moved and replaced with “a new cancer resulting from treatment of earlier cancer.”
 - “A potentially life-threatening condition, affecting less than 10% of the skin, in which the skin separates and peels off” and “A life-threatening condition, affecting more than 30% of the skin, in which the skin separates and peels off” have been moved replaced with “Blisters on the skin” and “Severe skin rash with blisters and peeling which can involve mouth and other parts of the body.”
 - The following risks have been added to be consistent with CTEP’s new condensed risk format for bendamustine:
 - “Pain at the site of injection”
 - “Swelling and redness at the site of the medication injection”
 - “Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions”
 - “Kidney damage which may cause swelling, may require dialysis”
 - “High blood pressure which may cause dizziness, blurred vision”
 - The following risks have been removed to be consistent with CTEP’s new condensed risk format for bendamustine:
 - “Difficulty sleeping or falling asleep”
 - “Nosebleed”
 - “Fever with dangerously low white cell count”

Risks and side effects related to Rituximab:

The risk list for rituximab has been updated to reflect the NCI’s new condensed risk profile format. The former “Likely” category has been replaced with “Common, Some May Be Serious,” the former “Less Likely” category has been replaced with “Occasional, Some May Be Serious,” and the former “Rare but Serious” has been replaced with “Rare, and Serious.”

- The following changes have been made within “Common, Some May Be Serious” to be consistent with CTEP’s new condensed risk format for rituximab:
 - “Fatigue” has been replaced with “Tiredness.”

- “Time away from work,” has been removed, as the risk is now included in the introductory language above all the risk lists.
- The following changes have been made within “Common, Some May Be Serious” to be consistent with CTEP’s new condensed risk format for rituximab:
 - “Decreased number of a type of white blood cell (neutrophil/granulocyte) which may lead to infection” has been replaced with “Increased chance of infection.”
 - “Decreased number of a type of blood cell that helps to clot blood (platelet) which may lead to increase in bruising or bleeding” has been replaced with “Bruising, bleeding.”
 - “Lack of enough red blood cells, which may cause tiredness or shortness of breath” has been replaced with “Anemia which may require blood transfusions.”
 - “Rash or itching” and “hives” have been combined to read, “Rash, itching or hives.”
 - “Diarrhea” and “vomiting” have been combined to read “Diarrhea, vomiting.”
 - “Stuffy nose” has been added to be consistent with CTEP’s new condensed risk format for rituximab.
 - The following risks have been removed to be consistent with CTEP’s new condensed risk format for rituximab:
 - “Seizures”
 - “Fluid retention in the arms or legs”
 - “Lung Inflammation” is now covered in the risk, “Severe life-threatening damage to the lungs” which appears under “Rare, and serious.”
- The following changes have been made within “Rare, and serious” to be consistent with CTEP’s new condensed risk format for rituximab:
 - “Rash which may become serious” has been changed to “Severe skin rash with blisters and peeling which can involve mouth and other parts of the body.”
 - The following risks have been added to be consistent with CTEP’s new condensed risk format for rituximab:
 - “Abnormal heartbeat”
 - “A tear or a hole in the stomach, or an obstruction, that may require surgery”

Research on Blood

- Under the bolded title “What kind of research will be done with my samples?”, the first sentence of the paragraph beneath the bullets has been revised to include a bone marrow specimen for the PP1 correlative. Additionally, the amount of blood to be collected has been corrected from “1 teaspoon” to “2 teaspoons.” The sentence now reads as follows: As part of this study researchers would like to collect about 2 teaspoons of blood and 1/5 teaspoon liquid bone marrow before you begin treatment, in addition to the blood and bone marrow that will be collected as a part your treatment.”
- Under “What are the risks of giving my samples for research?” the following text has been added as the second bullet: “There may be some temporary pain or discomfort associated with bone marrow aspirations and biopsies at the site where the needle is inserted. The side effects associated with obtaining bone marrow samples include pain at the site of the procedure, as well as possible bleeding, bruising or swelling. There is also a very small chance that you could develop an infection at the site of the procedure.”

A replacement protocol document and model consent have been issued.

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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

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

☒ **Update:**

☒ Eligibility changes

☒ Therapy / Dose Modifications / Study Calendar changes

☒ Informed Consent changes

☐ Scientific / Statistical Considerations changes

☒ Data Submission / Forms changes

☒ Editorial / Administrative changes

☐ Other :

☐ **Status Change:**

☐ Activation

☐ Closure

☐ Suspension / temporary closure

☐ Reactivation

IRB review and approval of this update is required within 90 days. Full board review is recommended. Please follow your local IRB guidelines. Patient re-consent is not required.

UPDATES TO THE PROTOCOL:

Cover Page

- On the bottom of the page, “Participating NCTN Groups” has been changed to “Participating Organizations.” Additionally, the full group names have been added for clarification.
- John Byrd has replaced Guido Marcucci as the Leukemia Correlative Science Committee Chair. Therefore, Dr. Marcucci has been removed from the cover page, and the following underlined text

has been added to Dr. Byrd's title: "Leukemia Correlative Study Co-Chair and Leukemia Correlative Science Committee Chair." Additionally, the formatting and order of the study team members has been slightly modified to accommodate these changes.

- Sumithra Mandrekar has replaced Susan Geyer as the Primary Statistician.

Schema

In the Arm 1 text box of the schema diagram, footnote "*" has been added after "Bendamustine 90 mg/m² IV, cycles 1 – 6, days 1 and 2 *." The footnote below the schema diagram reads: "At the treating investigator's discretion, the first cycle of bendmaustine may be given at 70 mg/m²." Subsequent footnotes have been relabeled accordingly.

Section 4.0 (Eligibility Criteria)

- The section has been reorganized and renumbered in order to specify pre-registration (step 0) and registration (step 1) eligibility criteria. Due to this, the following sentence has been removed from the beginning of the section "All patient eligibility criteria must be verified prior to registration (Step 1):"
- The following text has been inserted as the second and third paragraphs of the section:

"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)."

Section 4.1 (Pre-Registration Eligibility Criteria [Step 0])

This section and subsection 4.1.1 have been inserted to outline central Zap-70 sample submission required prior to registration.

Section 4.2 (Registration Eligibility Criteria [Step 1])

This section has been inserted to distinguish between pre-registration and registration eligibility criteria. The eligibility criteria that formerly appeared as Sections 4.1 – 4.16 appear in this section and have been renumbered as 4.2.1 – 4.2.16.

Section 4.2.8 (Formerly 4.8 - Active intercurrent disease)

In the third paragraph, the word "known" has been inserted before HIV as an HIV test is not required prior to registration. The sentence now reads: "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)."

Section 5.1.2 (Zap-70 Methylation)

In the second sentence, "OSU" has been corrected to "the Alliance Hematologic Malignancy Biorepository (HEME)." The sentence now reads: "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)."

Section 5.4.2 (Site credentialing for companion study A041202-EL1)

The last sentence of the section has been removed which read: "The Geriatric Assessment training module is found on the member side of the Alliance website, under 'education and training', 'online training.'" The following text has been added in its place to provide more detailed instructions:

“The training module may be accessed on the member side of the Alliance website (www.allianceforclinicaltrialsnoncology.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 the A041202 Protocol Coordinator.”

Section 5.5 (Stratification)

The following text has been added to the end of the section: “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.”

Section 5.6 (Re-Registration at the Time of Progression)

- The second sentence of the first paragraph has been modified to allow 12 months to crossover to Arm 2 after documentation of progression. The sentence now reads: “Please note that patients who opt to cross over must be re-registered to the study within 12 months of progression documentation.” Additionally, the following text has been inserted after the sentence: “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.”
- The following text has been inserted at the end of the first paragraph:

“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 6.2.4) as required for patients assigned to Arm 2 (unless specifically stated otherwise).”

Section 6.3 (Geriatric Assessment [Alliance A041202-EL1])

- In the table, the header “Submission Time Points (+/- 28 days)” has been changed to “Submission Time Points (+/- 30 days).”
- In the fourth column of the table, the “End of Cycle 6” submission time point has been changed to “Day 1 of Cycle 6.” This change was made in order to better align completion of the geriatric assessment with the study calendar, as patients are not required to be seen in between Day 1 of Cycle 6 and Day 1 of Cycle 9.
- In the second paragraph under the submission table, the second sentence has been modified to clarify that both patient completed questionnaire booklets and healthcare professional questionnaire booklets should be ordered through the CTSU. It now reads, “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.”

Section 7.0 (Required Data)

- Above the table and under the “To be completed within 30 DAYS before registration” header, the following text has been inserted as the second bullet, “Peripheral blood flow cytometry.”

- In the first bullet, under “To be completed within 14 DAYS before registration:” the following underlined text has been added: “All blood work except FISH analysis, peripheral blood flow cytometry, and central Zap-70.”
- In the table, footnote “**” has been added after the column header for “Relapse/Disease progression**.” Under the table, footnote “**” has been added that reads: “** 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.”
- In the third row of the table, the following underlined text has been added, “Physical examination and node measurements³.”
- In the table, subscript “1” has been added after “Laboratory Studies.” Additionally, the first sentence of footnote 1 has been modified to read: “Tests & observations and laboratory studies can be performed up to 48 hours prior to Day 1 of the specified cycle.”
- Footnote C has been reworded for clarification as follows: “Serum immunoglobulin should be performed 84 days (+/-7) after Day 1 of Cycle 6 for all patients. Then, perform yearly during follow-up for patients on continuous ibrutinib (Arms 2 and 3).”
- Footnote “D” has been modified to include a reference to bone marrow specimens for the LC1 correlative as follows: “In addition to institutional marrow, submit specimens for central morphology review (see Section 6.2.2) and A041202-LC1 correlative (see Sections 6.2.4 and 6.2.4.1).”
- In the table under “Staging,” in the row for bone marrow aspirate & biopsy, footnote “H” has replaced the letters that previously appeared in the columns for post-treatment follow up, 24 month follow up and relapse/disease progression. Under the table, footnote “H” has been added that reads: “For all patients, perform 84 days (+/- 7) after Day 1 of Cycle 6, at 24 month follow up and at relapse or disease progression. In addition to institutional marrow, submit bone marrow aspirate for A041202-LC1 as required in Sections 6.2.4 and 6.2.4.1.”

Section 8.0 (Treatment Plan)

The following paragraph has been inserted at the end of the section:

“It is acceptable for individual chemotherapy doses to be delivered \leq 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.”

Section 8.1 (Arm 1: Bendamustine/Rituximab)

The following text has been added to the end of the first paragraph of the section: “During cycle 1, at the discretion of the treating investigator, the bendamustine may be given at a dose of 70 mg/m² rather than 90. Subsequent cycles should be administered at 90 mg/m².”

Section 9.1 (Dose Modifications for Hematologic Toxicity)

In the first paragraph, the following underlined text has been added to the first sentence: “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.”

Section 9.2 (Dose Adjustments for Non-Hematologic Toxicity)

In the first bullet under the table, the following underlined text has been added to the last sentence, “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.”

Section 10.2.2 (Study Design)

In the third sentence, a submission time point for the geriatric assessments has been changed from “the end of cycle 6” to “day 1 of cycle 6.” This change was made in order to better align with the study calendar, as patients are not required to be seen in between Day 1 of Cycle 6 and Day 1 of Cycle 9. It now reads, “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.”

Appendix III (Registration Fatigue/Uniscale Assessment)

The following text has been inserted as the third paragraph: “A translator may be used to administer the assessment. Additionally, since NCIC is participating in A041202, a French version of the assessment has been provided on the following page.” In addition, the French Fatigue/Uniscale Assessment has been inserted as a second page of Appendix III.

Appendix V (Geriatric Assessment [A041202-EL1] Measures)

In both the patient and healthcare professional questionnaires, the “End of Cycle 6” assessment completion timepoint has been changed to “Day 1 of Cycle 6.” This change has been throughout the questionnaires.

UPDATES TO THE MODEL CONSENT:

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

- Under “Before you begin the study...”, a description of the Registration Fatigue/Uniscale Assessment has been added. This questionnaire is required for all patients who enroll on the study, but was mistakenly not described in the consent document. Specifically, the following text has been added: “The study researchers would also like to learn more about fatigue and quality of life. All study participants will be asked to complete a questionnaire with 2 questions. It will take less than one minute to complete the questions.”
- Under “During the study...”, the following underlined text has been added to the second bullet: “CT scan (chest, neck, abdomen & pelvis) at 3 months, 8 months and 24 months (2 years) after you start the treatment, and if your disease progresses (gets worse).” This text was added to be consistent with the third bullet.
- Under “During the study...”, the third bullet has been corrected to align with protocol requirements. Specifically, the incorrect mention of “biopsy” has been removed, and bone marrow aspirate requirements have changed from “9 months after you start the treatment” to “8 months after you start the treatment.” Additionally, “(2 years)” has been added after “24 months” to be consistent with the previous bullet in the section.

How long will I be in the study?

The following underlined text has been added to the last sentence of the section for clarity: “You will continue to be followed by your doctor for as long as you are taking the study drug (up to 10 years).”

Can I stop being in the study?

The following text was added to the end of the first paragraph: “If you discontinue treatment, you will be followed by your doctor every 3 months for up to 10 years.”

Related Research Studies

- Under “Geriatric Assessment,” in the first sentence of the second paragraph, the second time point for survey submission has been changed from “after cycle 6” to “at the beginning of cycle 6” to align with the change in submission schedule made with this update.
- Under “Making your Choice,” the following text has been removed as the brochure is not referenced in the new NCI model consent template: “To learn more, ask the study staff for the booklet called “Giving Samples for Research” or visit <http://www.cancer.gov>. You may want to read the section “What types of research use samples?” [If approved by IRB also include “Patient Information Brochure” in this statement.]”

A replacement protocol document and model consent have been issued.

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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

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

<input checked="" type="checkbox"/> Update:	<input type="checkbox"/> Status Change:
<input type="checkbox"/> Eligibility changes	<input type="checkbox"/> Activation
<input checked="" type="checkbox"/> Therapy / Dose Modifications / Study Calendar changes	<input type="checkbox"/> Closure
<input checked="" type="checkbox"/> Informed Consent changes	<input type="checkbox"/> Suspension / temporary closure
<input type="checkbox"/> Scientific / Statistical Considerations changes	<input type="checkbox"/> Reactivation
<input type="checkbox"/> Data Submission / Forms changes	
<input type="checkbox"/> Editorial / Administrative changes	
<input checked="" type="checkbox"/> Other :Ibrutinib CAEPR update	

The changes included in this update to Alliance A041202 have been made in response to the NCI Action Letter from Dr. Pamela Harris. This Action Letter is posted on the Alliance A041202 Study Page on the Alliance web site. A revised CAEPR with new risks has been added to the protocol. Therefore, the model consent form has been revised to incorporate these new risks consistent with the new NCI Model Consent Template instructions. There are no changes to the risk/benefit ratio.

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

UPDATES TO THE PROTOCOL:

Section 1.6 (Clinical Safety Update 2015)

Based on the updated ibrutinib protocol template provided by CTEP, this section has been added to include a summary of safety.

Section 1.7 (Risks)

Based on the updated ibrutinib protocol template provided by CTEP, this section has been added to provide information regarding ibrutinib risks and overdoses.

Section 3.0 (On Study Guidelines)

In the third bullet, the following underlined text has been added, “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.”

Section 9.2 (Dose Adjustments for Non-Hematologic Toxicity)

- In the fifth bullet, the following strikethrough text has been removed and underlined text added: “Patients who require the initiation of systemic anticoagulation should have ibrutinib held ~~for at least 5 days and up to 28 days~~ and be placed on a stable dose of low molecular weight heparin- (cConcomitant 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.”
- Two bullets have been added to the end of the section to provide dose modifications for atrial fibrillation and liver impairment.

Section 12.2 (CYP Inhibiting Drugs)

The following text has been added to the end of bullet #3, “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.”

Section 12.3 (Surgery)

- In the second bullet, “lumbar puncture [other than shunt reservoir access]” has been added as an example of a minor procedure.
- The following underlined text has been added to the last bullet, “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.”

Section 12.4 (Permitted Concomitant Medications)

Based on the updated ibrutinib protocol template provided by CTEP, this section has been added to provide information regarding permitted concomitant medications.

Section 12.5 (Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib)

Based on the updated ibrutinib protocol template provided by CTEP, this section has been added to provide guidance regarding potential interactions with P-gp or BCRP substrates.

Section 16.1(Expedited Adverse Event Reporting)

- CTEP-AERS reporting requirements for pregnancies and suspected pregnancies occurring in female patients has been modified from “during treatment and within 28 days after completion of treatment” to “during treatment and within 90 days after completion of treatment.”
- For neonatal deaths or complications, CTEP-AERS reporting requirements have been modified from “occurring within 28 days of birth independent of attribution” to “within 30 days of birth independent of attribution.” Therefore, the following sentence has also been modified as follows: “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.”

Section 16.2.1 (Ibrutinib [PCI-32765, NSC #748645])

The section has been modified to include the updated CAEPR (Version 2.3, October 7, 2015) provided by CTEP. Changes from Version 2.2 to Version 2.3 have been outlined below:

- Added New Risk:
 - Less Likely: Lymphocyte count increased
 - Rare but Serious: Blood and lymphatic system disorders - Other (leukostasis); Hepatic Failure; Stevens-Johnson syndrome; Treatment related secondary malignancy; Vascular disorders - Other (hemorrhage)
 - Also Reported on Ibrutinib Trials But With Insufficient Evidence for Attribution: Chest pain - cardiac; Cholecystitis; Immune system disorders - Other (systematic inflammatory response syndrome); Intracranial hemorrhage; Investigations - Other (increase CRP); Joint effusion; Leukoencephalopathy; Localized edema; Nervous system disorders - Other (PML); Pancreatitis; Pericarditis; Respiratory failure; Small intestinal obstruction; Ventricular tachycardia
- Increase in Risk Attribution:
 - Changed to Less Likely from Reported But With Insufficient Evidence for Attribution: Blurred vision; Dehydration; Febrile neutropenia; Leukocytosis; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (benign neoplasm of skin)
 - Changed to Rare but Serious from Reported But With Insufficient Evidence for Attribution: Acute kidney injury; Atrial fibrillation
- Decrease in Risk Attribution:
 - Changed to Rare but Serious from Less Likely: Hyperuricemia
 - Changed to Reported But Insufficient Evidence for Attribution from Less Likely: Abdominal pain; Dry mouth; Flatulence; Pruritus; Purpura
- Provided Further Clarification:
 - Footnote #2 has been added to Blood and lymphatic system disorders - Other (leukocytosis).
 - Footnote #4 has been added to Treatment related secondary malignancy.
 - Footnote #5 has been added to Vascular disorders - Other (hemorrhage).
 - Investigations - Other (pancytopenia) is now being reported as Blood and lymphatic system disorder - Other (pancytopenia)
 - Reproductive system and breast disorders - Other (vulvovaginal dryness) is now being reported as Vaginal dryness.
- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
 - Added: Cough; Infection; Neutrophil count decreased; Platelet count decreased
- Deleted Risk:
 - Also Reported on Ibrutinib Trials But With Insufficient Evidence for Attribution: Gastrointestinal disorders - Other (gingival edema); Gastrointestinal disorders - Other

(hypoesthesia oral); Musculoskeletal and connective tissue disorder - Other (medial tibial stress syndrome); Pharyngolaryngeal pain; Renal and urinary disorders - Other (dysuria); Skin and subcutaneous tissue disorders - Other (blood blister); Skin and subcutaneous tissue disorders - Other (onychoclasia)

Section 16.4 (Events of Special Interest)

This section has been added to provide additional expedited reporting requirements for major hemorrhagic adverse events.

Appendix VI (Child-Pugh Score)

This appendix has been added to include the Child-Pugh scoring system to be used for liver impairment dose modifications.

UPDATES TO THE MODEL CONSENT:

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

Based on the revisions to the Ibrutinib CAEPR described above, the NCI made the following changes to the condensed risk profile:

- Added New Risk:
 - Rare: Blood clot which may cause swelling; Liver damage which may cause yellowing of eyes and skin; Severe skin rash with blisters and can involve inside of mouth and other parts of the body; A new cancer resulting from treatment of earlier cancer
- Increase in Risk Attribution:
 - Changed to Occasional from Reported But With Insufficient Evidence for Attribution: Blurred vision; Dehydration; A new skin growth that is not cancerous
 - Changed to Rare from Reported But With Insufficient Evidence for Attribution: Kidney damage which may require dialysis; Abnormal heartbeat
- Decrease in Risk Attribution:
 - Changed to Reported But With Insufficient Evidence for Attribution from Occasionally (i.e., removed from the Risk Profile): Dry mouth; Passing gas; Itching
- Provided Further Clarification:
 - Infection (under Occasional) is now reported as Infection, especially when white blood cell count is low (under Occasional).

A replacement protocol document and model consent have been issued.

This study remains closed to new patient accrual.

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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

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

☒ **Update:**

☒ Eligibility changes

☒ Therapy / Dose Modifications / Study Calendar changes

☒ Informed Consent changes

☐ Scientific / Statistical Considerations changes

☒ Data Submission / Forms changes

☒ Editorial / Administrative changes

☐ Other :

☐ **Status Change:**

☐ Activation

☐ Closure

☐ Suspension / temporary closure

☐ Reactivation

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

- Ben Sanford has been removed as he is no longer a secondary statistician on this study.
- Luke Wilson has replaced Eva Hoke as the data manager and his contact information has been added.

Cover Page (2)

- The address for the Alliance Central Protocol Operations office has been updated.
- Eva Hoke and her contact information have been removed from this page as she is no longer the Data Manager for this study.
- Under “A041202 Pharmacy Contacts,” Ryan Daley’s e-mail address has been updated to ryan.daley@uvmhealth.org.

Cover Page (3)

A row has been removed from the Cancer Trials Support Unit table that contained the following text: “For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members’ website <https://www.ctsu.org> > education and resources tab > CTSU Operations Information > CTSU Regulatory and Monitoring Policy.”

Schema

- Above the study diagram the text, “Schema” and “1 cycle = 28 days” has been added.
- In the Arm 3 text box, the reference to footnote † has been removed.
- Footnote † has been changed from “One cycle is 28 days” to “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.”

Section 4.2 (Registration Eligibility Criteria[Step 1])

In Section 4.2.2 (Staging and Indication for Therapy), in the second bullet, the following strikethrough text has been removed and underlined text added: “High risk (formerly Rai stage III/IV) is defined by ~~fulfilling criteria for intermediate risk disease lymphocytosis with or without enlarged nodes and spleen~~ plus disease-related anemia (hemoglobin <11 g/dL) or thrombocytopenia (platelet count <100 x 10⁹/L) that is not attributable to autoimmune hemolytic anemia or thrombocytopenia.” This clarification has been made in order to correct misinterpretations about high risk patient eligibility.

Section 5.4 (Registration to Correlative Science Studies and Companion Protocols)

In Section 5.4.2 (Site Credentialing for Companion Study A041202-EL1), the following underlined text has been added to the end of the section, “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 e-mail documentation from the study team that states that the training was completed.”

Section 5.6 (Re-registration at the Time of Progression)

- In the first paragraph, a sixth sentence has been added to specify that patients do NOT need to meet the eligibility requirement of 5x10⁹ B lymphocytes in the peripheral blood for patient re-registration.
- In the first paragraph, a seventh sentence has been added to instruct sites to see Section 7.0 for other tests and observations that must be completed prior to re-registration.

Section 6.1 (Data Submission)

Section 6.1.1 (Data Submission Schedule and Requirements) has been added to provide guidance regarding data submission and requirements for this study. The new section also directs sites to helpful resources on the A041202 study page. The subsequent subsection has been renumbered accordingly.

Section 6.2 (Specimen Collection & Submission)

- The following underlined text has been added to the section title, “Specimen Collection & Submission.”

- In [Section 6.2.1 \(Specimen Submission Overview\)](#), the following changes have been made:
 - o The title of the section has been changed from “Specimen and Data Submission for Stratification” to “Specimen Submission Overview.” The specimen table previously found in Section 6.2.4 has been moved to the beginning of this section. As a result, references throughout the protocol to the table found in Section 6.2.4 have been updated to Section 6.2.1.
 - o In the header row, footnote “****” has been removed after “Day 1, Cycle 9” that read: “**** Day 1 of Cycle 9 should fall 84 days (+/- 7) after Day 1 of Cycle 6.” Throughout the protocol, references to “84 days (+/- 7) after Day of Cycle 6” have been changed to “Day 1 of Cycle 9.”
 - o With this update, the time points for testing and follow-up within the protocol have been converted to cycles instead of days, months, etc.. In the header row, the “Month 24” time point has been changed to “Day 1, Cycle 27.” This change has been made throughout the protocol document. Additionally, within the footnote “****” (formerly footnote “*****”), the following strikethrough text has been removed: “***** ~~Month 24 specimens should be collected and submitted approximately 730 days (+/- 10) from Day 1 of Cycle 1.~~ Required for all patients except those on Arm 1 who have crossed over to receive ibrutinib.....” Subsequent footnotes have been recategorized accordingly.
 - o The following strikethrough text has been removed from the second row of the table, “For ALL patients registered to A041202, submit the following ~~(for required correlative study A041202-LC1).~~”
 - o A row for central morphology review specimens has been added to the table under the second row, as it was previously only referenced in Section 6.2.2.
 - o The following underlined text has been added to footnote “*,” “* 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.”
 - o The following paragraph has been added to the end of the section: “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.”
- In [Section 6.2.4 \(Specimen Submission for Correlative Studies Alliance A041202-LC1 and Alliance A041202-PP1\)](#), the following changes have been made:
 - o The reference to “CALGB 9665” has been removed from the section title since the specimen submission overview table has been moved to Section 6.2.1.
 - o In [Section 6.2.4.1](#), [6.2.4.2](#), [6.2.4.3](#), the text “(For all patients)” has been added to the end of the section title.

Section 7.0 (Required Data)

The study calendar has been completely revised. Columns were combined and reorganized for readability and clarity and footnotes were modified. Changes to the requirements in this section include:

- Under “Pre-Study Testing Intervals,” the following changes have been made:
 - o CT scans and bone marrow biopsy have been moved under “To be completed within 30 days before registration.” Therefore, “To be completed within 28 DAYS before registration” has been removed.
 - o “HBsAg, HBsAb, Hep C, HB core antibody, Serum immunoglobulins and Beta 2 microglobulin” have been added under “To be completed within 30 days before registration.” Previously, these laboratory studies were required within 14 days before registration as they are considered “bloodwork.”
 - o Under “To be completed within 14 DAYS before registration,” the first bullet has been clarified by adding a parenthesis, and adding hepatitis antibodies, immunoglobulins, and beta 2

microglobulin as these laboratory studies can now be performed within 30 days before registration.

- Within the table and in the footnotes, the following changes were made:
 - o The columns for “Day 1 of Cycles 2, 3, 5 and 6” and “Day 1 of Cycle 4” have been combined. Therefore, a new footnote “G” has been added which states that Peripheral blood flow cytometry, serum immunoglobulins and CT scan are only required on Day 1 of Cycle 4 (not Day 1 of Cycles 2, 3, 5 and 6).
 - o The “Post-treatment follow-up*” column has been changed to “Day 1 of Every Third Cycle during Treatment, Arm 1 Observation & Clinical Follow-up*,**.” This column includes the Day 1 of Cycle 9 visit (formally known as the visit 84 Days after Day 1 of Cycle 6) and Cycle 27 visit (formally known as the Month 24 visit). Due to this the following changes have been made:
 - Footnote * was deleted; it stated “Post-treatment follow-up applies to all patients (including those patients who have completed treatment on Arm 1, those still continuing to receive ibrutinib and patients who have gone off protocol treatment.”
 - Footnote 2 was also removed which stated: “Month 24 follow-up should be completed approximately 730 days (+/- 10) from Day 1 of Cycle 1. For Arms 2 and 3, only for patients in continued remission; for Arm 1 patients who have crossed over to ibrutinib therapy, 24-month follow-up only for patients who have not experienced a second disease progression.”
 - A new footnote * was added to provide a larger window for Cycle 9 and Cycle 27 visits for those in clinical follow-up.
 - Footnote ** was added to provide an explanation of Arm 1 observation and clinical follow-up. Subsequent footnotes were recategorized accordingly.
 - o In the “Relapse/Disease Progression***” column, footnote *** was added to highlight that the studies are required for both first and second progressions (i.e. for patients who have crossed over to receive ibrutinib). Subsequent footnotes have been renumbered.
 - o A new column was created for “Prior to re-registration****.” Footnote **** (formally footnote **) was revised to provide more clear instructions for patient crossover.
 - o Within the table, under “Laboratory Studies,” PT INR has been added in the same row as AST, ALT due to the dose modifications for liver impairment and Child-Pugh scoring system that were added with Update #03.
 - o Footnote “C” has been revised. The following strikethrough text has been removed and underlined text added: “Serum immunoglobulins should be performed ~~84 days (+/- 7) after Day 1 of Cycle 6~~ 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 during follow-up for patients on continuous ibrutinib (Arms 2 and 3).”
 - o A reference to footnote 2 has been added after “FISH for del(11q22.3) and del (17p13.1) (performed locally)” under the Laboratory Studies header. Footnot 2 has been added below the table that reads: “FISH can be performed on peripheral blood (preferred) or bone marrow.”
 - o The following text has been added to footnote “3”: “Bilateral measurements of largest nodes on CT are required.”

Section 9.2 (Dose Adjustments for Non-Hematologic Toxicity)

- The following text has been added to the end of the third bullet: “At the discretion of the treating physician and with study chair approval, rituximab and/or bendamustine can be discontinued for severe infusion reactions.”
- The following text has been added as a new bullet to the end of the section: “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.”

Section 13.1 (Response Criteria)

- In Section 13.1.1 (Complete Response...), the following text has been added as the last bullet of the section: “Patients who fulfill the criteria of CR with exception of not having a bone marrow biopsy performed will be considered a clinical CR.”
- In Section 13.1.3 (Progressive Disease...), the following text has been added as the first bullet of the section: “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).”

Section 14.1 (Duration of Treatment)

- In Section 14.1.1 (CR, PR, or SD), the following changes have been made:
 - o In “Arm 1,” follow-up has been corrected from “every 3 months” to “every 3 cycles.” Additionally, the paragraph has been revised to provide a description of “Arm 1 Observation” and the follow-up that is required. Patients must go on to Arm 1 Observation if they were assigned to Arm 1 and wish to crossover to ibrutinib upon disease progression.
 - o Under “Arm 2,” the following text has been added at the end of the paragraph: “...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.”
 - o Under “Arm 3,” the following text has been added at the end of the paragraph: “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.”
- Section 14.1.3 (Follow Up Schedule) has been completely revised to better outline patient follow-up for patients who have completed protocol treatment and for those who discontinue for progression or other reasons.
- Section 14.1.4 (Follow-up schedule for ineligible patients registered to the trial) has been added to detail procedures for patients deemed ineligible after study randomization.

Section 16.1 (Expedited Adverse Event Reporting)

- The second paragraph has been removed that instructed institutions to route all expedited adverse event reports through the Alliance Central Protocol Operations Program Office. CTEP-AERS reports are automatically be forwarded to the Alliance so this step is unnecessary.
- In the table, in the second to last cell, a note has been added that states: “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.”
- Under “Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 3 Trials Utilizing an Agent Under an IND;,” the third bullet has been removed that excluded deaths clearly due to progressive disease from CTEP-AERS reporting requirements. This is not correct, all deaths, even those clearly due to progressive disease are required to be submitted as an adverse event via CTEP-AERS.

Appendix II

Phenytoin has been bolded as it is a strong CYP3A4/5 inducer.

Appendix V

In the “Healthcare Professional Questionnaire” under the “Healthcare Professional Information Sheet,” the text “Page 1 of 6” has been corrected to “Page 1 of 5.”

UPDATES TO THE MODEL CONSENT:

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

In the second bullet under “You will need these tests and procedures that are not part of regular cancer care because you are in this study,” the timing of the Cycle 9 Day 1 blood tests have been corrected from “9 months after you start treatment” to “8 months...” for consistency. Additionally, in the same sentence, the following underlined text has been added for consistency “24 months (2 years) after you start treatment....”

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

At the end of this section, under reproductive risks, the following underlined text has been added: “Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study and for 90 days after your last dose of study drug.” This language was updated to be consistent with information that was previously added to the protocol with Update #03.

A replacement protocol document and model consent have been issued.

This study remains closed to new patient registration.

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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

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

- | | |
|---|---|
| <input checked="" type="checkbox"/> Update: | <input type="checkbox"/> Status Change: |
| <input type="checkbox"/> Eligibility changes | <input type="checkbox"/> Activation |
| <input checked="" type="checkbox"/> Therapy / Dose Modifications / Study Calendar changes | <input type="checkbox"/> Closure |
| <input checked="" type="checkbox"/> Informed Consent changes | <input type="checkbox"/> Suspension / temporary closure |
| <input type="checkbox"/> Scientific / Statistical Considerations changes | <input type="checkbox"/> Reactivation |
| <input type="checkbox"/> Data Submission / Forms changes | |
| <input type="checkbox"/> Editorial / Administrative changes | |
| <input checked="" type="checkbox"/> Other :Ibrutinib CAEPR update | |

The changes included in this update to Alliance A041202 have been made in response to the NCI Action Letter from Dr. S. Percy Ivy, dated November 30, 2016. This Action Letter is posted on the Alliance A041202 Study Page on the Alliance web site. A revised CAEPR with new risks has been added to the protocol. Therefore, the model consent form has been revised to incorporate these new risks consistent with the new NCI Model Consent Template instructions. There are no changes to the risk/benefit ratio.

Expedited review is allowed. IRB approval (or disapproval) is required within 90 days. Please follow your IRB of record guidelines. Please follow the policy of your IRB of record regarding notifying patients of new information contained in this update.

UPDATES TO THE PROTOCOL:

Section 9.2 (Dose Adjustments for Non-Hematologic Toxicity)

The following text has been added as the ninth bullet: “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.”

Section 16.1 (Expedited Adverse Event Reporting)

Under “Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 3 Trials Utilizing an Agent Under an IND,” the following text has been added as the fourth bullet: “All suspected and confirmed cases of fungal infections should be reported to CTEP within 24 hours.”

Section 16.2 (Comprehensive Adverse Events and Potential Risks [CAEPR])

Section 16.2.1 (Ibrutinib [PCI-32765, NSC#748645]) has been modified to include the updated CAEPR (Version 2.4, October 12, 2016) provided by CTEP. Changes from Version 2.3 to Version 2.4 have been outlined below:

- The SPEER grades have been updated.
- **Added New Risk:**
 - **Rare but Serious:** Infection and infestations - Other (bronchopulmonary and central nervous system fungal infections); Skin and subcutaneous tissue disorders - Other (angioedema)
 - **Also Reported on Ibrutinib Trials But With Insufficient Evidence for Attribution:** Atrioventricular block complete; Blood and lymphatic system disorders - Other (hemorrhagic diathesis); Blood and lymphatic system disorders - Other (lymphadenitis); Cheilitis; Cystitis noninfective; Depressed level of consciousness; Encephalopathy; Flank pain; Gastrointestinal disorders - Other (gluteal intramuscular bleed); General disorders and administration site conditions - Other (multiple organ dysfunction syndrome); Myocardial infarction; Nail loss; Palpitations; Pericardial effusion; Periodontal disease; Reversible posterior leukoencephalopathy syndrome; Skin and subcutaneous tissue disorders - Other (onychoclasia); Skin atrophy; Supraventricular tachycardia; Thromboembolic event
- **Increase in Risk Attribution:**
 - **Changed to Likely from Less Likely:** Neutrophil count decreased
 - **Changed to Less Likely from Rare but Serious:** Atrial fibrillation; Vascular disorders - Other (hemorrhage)
 - **Changed to Less Likely from Also Reported on Ibrutinib Trials But With Insufficient Evidence for Attribution:** Abdominal pain; Hypertension
 - **Changed to Rare but Serious from Also Reported on Ibrutinib Trials But With Insufficient Evidence for Attribution:** Allergic Reaction; Hypotension; Peripheral sensory neuropathy; Tumor lysis syndrome
- **Decrease in Risk Attribution:**
 - **Changed to Rare but Serious from Less Likely:** Leukocytosis
 - **Changed to Also Reported on Ibrutinib Trials But With Insufficient Evidence for Attribution from Less Likely:** Dyspepsia

- Deleted Risk:
 - Also Reported on Ibrutinib Trials But With Insufficient Evidence for Attribution: Creatinine increased; Dry mouth; Dry skin; Edema face; Lethargy; Malaise; Rash acneiform
- Provided Further Clarification:
 - The Footnotes have been renumbered.
 - Rash maculo-papular (under Less Likely) is now reported as Skin and subcutaneous tissue disorders - Other (Rash) (under Less Likely).
 - Epistaxis, Gastrointestinal hemorrhage, Hematoma. Intracranial hemorrhage, Purpura, Vaginal hemorrhage (all under Also Reported on Ibrutinib Trials But With Insufficient Evidence for Attribution) are now being reported under Vascular disorders Other (hemorrhage) (under Less Likely).
 - Footnote #4 has been added to Infection and infestations - Other (bronchopulmonary and central nervous system fungal infections) and reads as follows, “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.”
 - Footnote#6 has been added to Skin and subcutaneous tissue disorders - Other (angioedema) and reads as follows, “Angioedema may be seen in association with the immune-related adverse event of anaphylaxis.”
 - Footnote #7 has been added to Skin and subcutaneous tissue disorders - Other (Rash) and reads as follows, “Rash may include but not limited to the terms dermatitis, erythema, rash generalized, rash maculo-papular, rash pustular, rash pruritic, and urticaria.”
 - Footnotes #5 and #6 on the previous CAEPR version have been updated and combined into footnote # 8, which now reads, “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 limited to Intracranial hemorrhage, Intraventricular hemorrhage, and Subdural hematoma), Ecchymoses, Purpura (petechia), Gastrointestinal hemorrhage (including but not limited to Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage), Genitourinary tract hemorrhage (including but not limited to Hematuria and Vaginal hemorrhage), Respiratory tract hemorrhage (including but not limited to epistaxis), and Spontaneous hemorrhage.”

UPDATES TO THE MODEL CONSENT:

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

Based on the revisions to the Ibrutinib CAEPR described above, the NCI made the following changes to the condensed risk profile (found under “Risks and side effects related to ibrutinib include those which are”):

- Added New Risk:
 - Rare: Fungal infection of the lungs and/or central nervous system which may cause cough, shortness of breath, fever, changes in thinking, dizziness or pain in neck or head

- Increase in Risk Attribution:
 - Changed to Occasional from Rare: Abnormal heartbeat
 - Changed to Occasional from Also Reported on Ibrutinib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): High blood pressure
 - Changed to Rare from Also Reported on Ibrutinib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat; Low blood pressure which may cause feeling faint; Numbness, tingling or pain of the arms and legs
- Decrease in Risk Attribution:
 - Also Reported on Ibrutinib Trials But With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Heartburn

A replacement protocol document and model consent have been issued.

This study remains closed to new patient accrual.

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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)

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<input checked="" type="checkbox"/> Update:	<input type="checkbox"/> Status Change:
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<input type="checkbox"/> Data Submission / Forms changes	
<input type="checkbox"/> Editorial / Administrative changes	
<input checked="" type="checkbox"/> Other :Ibrutinib CAEPR update	

The changes included in this update to Alliance A041202 have been made in response to the NCI Action Letter from Dr. S. Percy Ivy, dated August 7, 2017. This Action Letter is posted on the Alliance A041202 Study Page on the Alliance web site. A revised CAEPR with new risks has been added to the protocol. Therefore, the model consent form has been revised to incorporate these new risks consistent with the new NCI Model Consent Template instructions. There are no changes to the risk/benefit ratio.

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

UPDATES TO THE PROTOCOL:

Section 16.2 (Comprehensive Adverse Events and Potential Risks [CAEPR])

[Section 16.2.1 \(Ibrutinib \[PCI-32765, NSC#748645\]\)](#) has been modified to include the updated CAEPR (Version 2.5, May 25, 2017) provided by CTEP. Changes from Version 2.4 to Version 2.5 have been outlined below:

- Added New Risk:
 - Rare but Serious: Sudden death NOS; Ventricular arrhythmia; Ventricular fibrillation
 - Increase in Risk Attribution:
 - Changed to Rare but Serious from Also Reported on Ibrutinib Trials but with Insufficient Evidence for Attribution: Ventricular tachycardia.
-

UPDATES TO THE MODEL CONSENT:

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

Based on the revisions to the Ibrutinib CAEPR described above, the NCI has made the following changes to the condensed risk profile (found under “Risks and side effects related to ibrutinib include those which are”):

- Added New Risk:
 - Rare: Death
- Provide further clarification:
 - Abnormal heartbeat (under Occasional) is now reported as Abnormal heartbeat which may cause fainting (under Occasional).
 - Sores in mouth which may cause difficulty swallowing (under Occasional) is now reported as Sores in the mouth which may cause difficulty swallowing (under Occasional).
 - Blood clot which may cause swelling (under Rare) is now reported Blood clot (under Rare).
 - Liver damage which may cause yellowing of eyes and skin (under Rare) is now reported as Liver damage which may cause yellowing of eyes and skin, swelling (under Rare).
 - Fungal infection of the lungs or central nervous system which may cause cough, shortness of breath, fever, changes in thinking, dizziness or pain in neck or head (under Rare) is now reported as Fungal infection of the lungs or central nervous system which may cause cough, shortness of breath, fever, confusion, headache or stiff neck (under Rare).
 - “Severe skin rash with blisters and can involve inside of mouth and other parts of the body” (under Rare) is now reported as “Severe skin rash with blisters and peeling which can involve mouth and other parts of the body” (under Rare).
 - Low blood pressure which may cause feeling faint (under Rare) is now reported as Low blood pressure (under Rare).

A replacement protocol document and model consent have been issued.

This study remains closed to new patient accrual.

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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

<input checked="" type="checkbox"/> Update:	<input type="checkbox"/> Status Change:
<input type="checkbox"/> Eligibility changes	<input type="checkbox"/> Activation
<input type="checkbox"/> Therapy / Dose Modifications / Study Calendar changes	<input type="checkbox"/> Closure
<input checked="" type="checkbox"/> Informed Consent changes	<input type="checkbox"/> Suspension / temporary closure
<input type="checkbox"/> Scientific / Statistical Considerations changes	<input type="checkbox"/> Reactivation
<input type="checkbox"/> Data Submission / Forms changes	
<input checked="" type="checkbox"/> Editorial / Administrative changes	
<input checked="" type="checkbox"/> Other :Ibrutinib CAEPR update	

The changes included in this update to Alliance A041202 have been made in response to the NCI Action Letter from Dr. S. Percy Ivy. This Action Letter is posted on the Alliance A041202 Study Page on the Alliance and CTSU websites. A revised CAEPR with new risks has been added to the protocol. Therefore, the model consent form has been revised to incorporate these new risks consistent with the new NCI Model Consent Template instructions. There are no changes to the risk/benefit ratio.

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

UPDATES TO THE PROTOCOL:

Protocol Resources

- In the “Protocol-related questions” table, the contact for CTEP-AERS reporting questions has been updated to the “Pharmacovigilance Inbox.”
- The Document History table has been removed. This table now appears as a separate document on the study-specific webpages.

Section 6.1 (Data Submission)

In [Section 6.1.2](#) (Adverse Event Data Submission), the following has been added to the end of the first paragraph: “**Note:** CTCAE version 5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018 (see [Section 16.1](#)).”

Section 16.1 (Expedited Adverse Event Reporting)

- In the first paragraph, the last 3 sentences have been updated to reflect the transition to CTCAE version 5.0 for expedited reporting.
- Under “Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements,” the 5th and 6th bullet points have been updated to align with AE reporting in CTCAE version 5.0.

Section 16.2 (Comprehensive Adverse Events and Potential Risks [CAEPR])

[Section 16.2.1](#) (Ibrutinib [PCI-32765, NSC#748645]) has been modified to include the updated CAEPR (Version 2.6, January 29, 2018) provided by CTEP. Changes from Version 2.5 to Version 2.6 include the following:

- The SPEER grades have been updated.
- The section below utilizes CTCAE 5.0 language unless otherwise noted.
- Increase in Risk Attribution:
 - Changed to Rare but Serious from Also Reported on Ibrutinib Trials but with Insufficient Evidence for Attribution: Pneumonitis
- Provided Further Clarification:
 - The following footnote #6 was added: “Pneumonitis is included in the group term Interstitial Lung Disease (ILD) which also includes lung infiltration, bronchiolitis, pulmonary fibrosis, eosinophilic pneumonia, pulmonary toxicity, and alveolitis allergic.”
 - Musculoskeletal and connective tissue disorders - Other (muscle spasms) (*CTCAE 4.0 language*) is now reported as Muscle cramp.
 - Conjunctivitis, previously listed under the EYE DISORDERS SOC (*CTCAE 4.0 language*), is now listed under the INFECTIONS AND INFESTATIONS SOC.
 - Eye disorders - Other (visual acuity reduced) (*CTCAE 4.0 language*) is now reported as Vision decreased.
 - Infusion related reaction, previously listed under the GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS SOC (*CTCAE 4.0 language*), is now listed under the INJURY, POISONING AND PROCEDURAL COMPLICATIONS SOC.
 - Metabolism and nutrition disorders - Other (hyperphosphatemia) (*CTCAE 4.0 language*) is now reported as Hyperphosphatemia.
 - Metabolism and nutrition disorders - Other (fluid retention) (*CTCAE 4.0 language*) is now reported as Generalized edema under the GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS SOC.
 - Agitation, previously listed under the NERVOUS SYSTEM DISORDERS SOC (*CTCAE 4.0 language*), is now listed under the PSYCHIATRIC DISORDERS SOC.

- Sinus pain, previously listed under the NERVOUS SYSTEM DISORDERS SOC (*CTCAE 4.0 language*), is now listed under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.
- Periorbital edema, previously listed under the SKIN AND SUBCUTANEOUS TISSUE DISORDERS SOC (*CTCAE 4.0 language*), is now listed under the EYE DISORDERS SOC.

UPDATES TO THE MODEL CONSENT:

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

Based on the updated CAEPR described above, the following changes have been made to the NCI condensed risk profile for ibrutinib (found under “Risks and side effects related to ibrutinib include those which are”):

- Increase in Risk Attribution:
 - Changed to Rare from Also Reported on Ibrutinib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Damage to lungs which may cause shortness of breath
- Provided Further Clarification:
 - Muscle spasms (under Occasional) is now reported under Pain (under Occasional).

A replacement protocol document and model consent have been issued.

This study remains closed to new patient accrual.

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