Update #09

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A051301

A RANDOMIZED DOUBLE-BLIND PHASE III STUDY OF IBRUTINIB DURING AND FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION VERSUS PLACEBO IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA OF THE ACTIVATED B-CELL SUBTYPE

NCI-supplied agent(s): Ibrutinib (NSC #748645, [redacted]); IND holder: NCI-CTEP
Commercial agent(s): BCNU (Carmustine) (NSC# 409962), Etoposide (NSC# 141540), Ara-C (Cytarabine) (NSC# 63878), Melphalan (NSC# 8806), Cyclophosphamide (NSC#26271)

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

If your site utilizes the CIRB as your IRB of record for this study, no recommended level of IRB review is provided by the Alliance. This amendment must be implemented within 30 days after posting. Please refer to the CIRB amendment application and CIRB guidelines for further instructions.

If your site utilizes a local IRB as your IRB of record for this study, IRB approval (or disapproval) is required within 90 days. Expedited IRB Approval is allowed. Please follow your local IRB guidelines.

UPDATES TO THE PROTOCOL:

Cover Page

- [redacted] has been removed from the cover page.
- [redacted] has replaced [redacted] as the Transplant Committee Chair.
- [redacted] has been removed from the cover page.
- [redacted] has replaced [redacted] as the Primary Statistician.

Study Resources
The contact information for the Alliance Biorepository at Washington University has been updated.

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

Schema Page 3
- In the "Study Procedures" column, the continuation timing has been changed to "day +30 to +75."
- In footnote 3, the 21 day window has been changed to 45 days.

Section 3.3 (Eligibility Criteria [Step 1])
In Section 3.3.4 (Prior Treatment), the following has been added to the second criterion: "Prior CART therapy is allowed and counts as one line of therapy."

Section 4.2 (Cancer Trials Support Unit Registration Procedures)
This section has been updated with the current CTSU template language.

Section 4.5 (Patient registration/randomization procedures)
This section has been updated with the current CTSU template language.

Section 5.0 (Study Calendar)
- The two columns under "Cycles 2-13" have been combined.
- The requirement for the BM biopsy prior to registration has been removed.
- In footnote #, the ≤ 21 day window has been changed to ≤ 30 days.
- In footnote **, the first sentence has been revised to read: "Treatment assessment on Day 1 and Day 15 of Cycle 2 and Day 1 of Cycles 3 through 13 can be performed outside the study/transplant center, provided the results are made available to the treating study investigator."
- In footnote **, the +/- 4 day window has been changed to +/- 7 days.
- The former footnote *** has been removed.
- In footnote 2, the ≤ 21 day window has been changed to ≤ 45 days.
- Footnote 10 has been revised as follows: "Bone marrow biopsy and aspirate ~~per institutional standards within 84 days (12 weeks) prior to registration. Repeat~~ performed for response assessment at 3 months only if positive prior to registration or if there is a clinical concern."
- In the "Crossover Phase" study calendar, in footnote *, the +/- 4 day window has been changed to +/- 7 days.
- In the "Crossover Phase" study calendar, in footnote 2, the ≤ 21 day window has been changed to ≤ 28 days.

Section 6.1 (Data Collection and Submission)
This section has been updated with the current CTSU template language.

Section 7.0 (Treatment Plan/Intervention)
In the first sentence, the 21 day window has been changed to 45 days.

Section 7.3 (Continuation)
In the first sentence, "Day +60" has been changed to "Day +75."

Section 13.1 (Study Design)
This section has been updated to reflect the revised sample size with this amendment.

Section 13.2 (Sample Size, Accrual Time and Study Duration)
This section has been updated to describe the rationale for the sample size and statistical design changes being made with this amendment.

Section 13.5 (Interim Analysis Design for Primary Endpoint)
This section has been completely revised to reflect the updated statistical design with this amendment.

Section 13.6 (Analysis Plan for Secondary Endpoints)
This section has been completely revised to reflect the updated statistical design with this amendment.

Section 13.9 (Inclusion of Women and Minorities)

- The enrollment table has been updated to reflect the revised sample size.
- The ethnic and racial categories have been removed from under the enrollment table to align with the current Alliance model protocol template.

Section 14.1 (Imaging Correlative Science)
Section 14.1.4 (Statistical Design) has been revised to reflect the updated statistical design and sample size for the main study.

Section 14.2 (Pharmacogenetics [Alliance A051301-PP1])
In Section 14.2.4 (Statistical Design), the second paragraph has been revised to reflect the updated sample size of the main study.

Section 14.3 (Biomarkers studies in Alliance A051301 [Alliance A051301-ST1])

- In Section 14.3.1 (BCR Mutational Analysis), the "Statistical Design" section has been revised to reflect the updated statistical design and sample size for the main study.
- In Section 14.3.2 (BCL2 and MYC assessment prognostic markers), the "Statistical Design" section has been revised to reflect the updated statistical design and sample size for the main study.

UPDATES TO THE EARLY SAFETY MODEL CONSENT:

No changes have been made to the Early Safety model consent.

UPDATES TO THE RANDOMIZED STUDY MODEL CONSENT:

Why is this study being done?
The last sentence has been revised to read: "There will be about 160 people with "ABC" subtype DLBCL taking part in this study."

Replacement protocol and model consent documents have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A051301/BMT CTN 1201

A RANDOMIZED DOUBLE-BLIND PHASE III STUDY OF IBRUTINIB DURING AND FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION VERSUS PLACEBO IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA OF THE ACTIVATED B-CELL SUBTYPE

This study is open to FACT-accredited institutions only.

NCI-supplied agent(s): Ibrutinib (NSC #748645, IND #117241); IND holder: NCI-CTEP
Commercial agent(s): BCNU (Carmustine) (NSC# 409962), Etoposide (NSC# 141540), Ara-C (Cytarabine) (NSC# 63878), Melphalan (NSC# 8806), Cyclophosphamide (NSC#26271)

ClinicalTrials.gov Identifier: NCT02443077

Alliance Study Chair
[redacted]
University of California, San Francisco
400 Parnassus Ave
San Francisco, CA 94143
Tel: [redacted] Fax: [redacted]

BMT CTN Study Chair
[redacted]
Medical College of Wisconsin
9200 West Wisconsin Ave
Milwaukee, WI 53226
Tel: [redacted] Fax [redacted]

Lymphoma Committee Chair
[redacted]

Transplant Committee Chair
[redacted]

Pathology Committee Chair and Correlative Co-Chair
[redacted]

Correlative Study Co-Chair
[redacted]

ECOG-ACRIN Co-Chair
[redacted]

SWOG Co-Chair
[redacted]

Community Oncology Co-Chair
[redacted]

Imaging Co-Chair
[redacted]

Primary Statistician
[redacted]

Secondary Statistician
[redacted]

Correlative Statistician
[redacted]

Protocol Coordinator
[redacted]

Data Manager
[redacted]

Participating NCTN Organizations:
ALLIANCE/Alliance for Clinical Trials in Oncology, **ECOG-ACRIN**/ECOG-ACRIN Cancer Research Group, **NRG**/NRG Oncology, **SWOG**/SWOG, **BMT-CTN**/Blood and Marrow Transplant Clinical Trials Network

Study Resources:

Expedited Adverse Event Reporting https://eapps-ctep.nci.nih.gov/ctepaers/	**Medidata Rave® iMedidata portal** https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	**Biospecimen Management System** http://bioms.allianceforclinicaltrialsinoncology.org

Protocol Contacts:

A051301 Nursing Contact
[redacted]
Tel: [redacted]
E-mail: [redacted]

A051301 Pharmacy Contact
[redacted]
Tel: [redacted]
Email [redacted]

Alliance Biorepository at Washington University (WUSTL)
BJC Institute of Health
425 S. Euclid Ave., Room IH-05-135
St. Louis, MO 63110
Tel: [redacted]
alliance@email.wustl.edu

A051301 Imaging Contact
IROC
The Ohio State University
Wright Center of Innovation
395 W. 12th Ave. [redacted]
Columbus, OH 43210
Tel: [redacted] Fax: [redacted]
Alliance051301@irocohio.org

Frederick National Laboratory PI
[redacted]
Frederick National Laboratory for Cancer Research
8560 Progress Drive ATRF C3015
Frederick, MD 21701
Tel: [redacted]

Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox *regulatory@allianceNCTN.org*
Questions regarding CTEP-AERS reporting:	Pharmacovigilance Inbox *pharmacovigilance@allianceNCTN.org*
Questions regarding specimens/specimen submissions:	appropriate Alliance Biorepository

CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION

For regulatory requirements:	For patient enrollments:	For data submission:
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. Do not submit study data or forms to the CTSU. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (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 log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e. patient eligibility or treatment-related) see Protocol Contacts, Page 2.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

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Pre-Registration Eligibility Criteria

- Central pathology review submission (see section 3.2.1)

Eligibility Criteria (see section 3.3)

- Diagnosis of DLBCL, non-GCB (see section 3.3.1)
- Eligible for high-dose chemotherapy and AutoHCT (see section 3.3.2)
- Adequate organ function for transplant (see section 3.3.3)
- Progressed or refractory to prior anthracycline-containing chemotherapy (see section 3.3.4)
- ≤ 3 prior regimens for large cell component (see section 3.3.4)
- Chemosensitive disease (see section 3.3.4)
- Not pregnant and not nursing (see section 3.3.5)
- Age ≥ 18 years
- No chronic use of strong or moderate CYP3A inhibitors or strong CYP3A inducers (see section 3.3.7)
- Intercurrent or recent Illness (see section 3.3.8)
- ECOG performance status ≤ 2

Required Initial Laboratory Values
(See also section 3.3.3)

Creatinine	≤ 2.0 mg/dL
OR Calc. Creatinine Clearance by Cockcroft-Gault	≥ 40 mL/min
Total Bilirubin	≤ 1.5 x ULN*
AST/ALT	≤ 3 x ULN
PT/INR	< 1.5 x ULN
PTT (aPTT)	< 1.5 x ULN

**Unless isolated hyperbilirubinemia attributed to Gilbert's syndrome*

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STUDY TIMELINE

Approximate Timing	Clinical Procedures	Study Procedures
3-16 weeks pre AutoHCT	Salvage chemotherapy	Pre-registration for central review [1]
2-3 weeks pre AutoHCT	Stem cell collection	Registration[2] (see section 4.0)
5 weeks	AutoHCT	Conditioning regimen (Cycle 1)[3]: BEAMi or CBVi
12 months		Continuation (Cycles 2-13): Continuation to start day +30 to +75
24 months		Follow up for PFS24 (primary endpoint)
60 months		Long-term follow up

1 Central review will consist of confirmation of diagnosis and determination of non-GCB. Turnaround time will be approximately 5 business days.
2 Following registration, it will take 7-10 days for ibrutinib to arrive at local site.
3 Conditioning regimen (Cycle 1) is to begin ≤ 45 days following registration.

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1.0 BACKGROUND

Diffuse Large B-cell Lymphoma (DLBCL) is the most common lymphoma worldwide. Even though rituximab/anthracycline-containing chemotherapy (e.g. R-CHOP) can cure a significant proportion of patients with this disease in the modern era, approximately 40% are either refractory to front-line treatment or relapse following therapy [1-3]. Gene expression profiling has identified two distinct subtypes of DLBCL with a differential response to front-line chemotherapy [4, 5]. The two main subtypes originally identified, germinal center B-cell-like (GCB) and activated B-cell-like (ABC)[1] have dramatically different 5-year survival rates of 60% versus 35% after CHOP respectively. At the time of relapse, regardless of disease subtype, the standard of care involves salvage chemotherapy followed by autologous hematopoietic cell transplantation (AutoHCT) in chemosensitive patients.[6] With this approach, 24-month progression-free survival (PFS) following transplantation in the rituximab era approaches 48% and 24-month overall survival (OS) 65%.[7-9] Disease progression or relapse following AutoHCT is the major cause of mortality in this patient population. The majority of relapses (~70%) occur in the first 12 months following AutoHCT [9]. The current study was thus designed to improve survival outcomes in this patient population by incorporating biologically targeted therapy in the treatment program.

Patients with relapsed DLBCL in the rituximab era have poor outcomes with conventional standard approaches to AutoHCT. Additionally, patients with the ABC subtype of DLBCL as defined by either mRNA or protein methods have proven inferior outcomes in the front-line setting with standard chemotherapy approaches and differential response to salvage therapies in the relapsed/refractory setting. Ibrutinib is a selective inhibitor of BTK, a critical component of the chronic active BCR signaling pathway, which plays a central role in the pathogenesis of ABC DLBCL. Our hypothesis is that the addition of ibrutinib, which as a single agent is clinically active in the relapsed/refractory setting of ABC DLBCL, will augment transplant effectiveness and target residual low-burden disease thus leading to an improvement in 24-month PFS and OS in this patient population. This is a randomized placebo-controlled phase III study that will evaluate ibrutinib therapy during and following AutoHCT in this high-risk patient population. This approach is novel in selectively targeting the ABC subtype of disease using a biologically relevant small molecule inhibitor in combination with high-dose therapy. In this regard, this approach can make a major contribution to the treatment of patients with relapsed DLBCL.

[1]*For the purpose of this discussion, the terms non-GCB and ABC will be used interchangeably.*

1.1 DLBCL Biology: Cell of Origin Subtypes

The Lymphoma/Leukemia Molecular Profiling Project at the NCI (LLMPP) has used molecular profiling to subdivide diffuse large B-cell lymphoma into distinct subtypes with a differential response to front-line chemotherapy [4, 5]. The two main subtypes originally identified, germinal center B-cell-like (GCB) and activated B-cell-like (ABC) have dramatically different 5-year survival rates of 60% versus 35% respectively. A multivariate predictive model of overall survival was created from 27 genes chosen from different functional groups differentially expressed in the two subtypes [5]. This gene expression- based outcome predictor was able to stratify patients into risk groups with strikingly distinct overall survival rates. One half of the patients could be placed in a favorable risk group (GCB) with a 71% 5-year survival rate. One quarter of the patients were in a poor risk group with only a 15% 5-year survival rate and the remaining quarter of patients had a 36% 5-year survival rate [10]. These results have been extended to the protein level by immunohistochemistry, with several classifier algorithms since developed that retain predictive ability, even though they exhibit variable cross-correlation. [11-13] Moreover, this biological separation, as captured by GEP or IHC profiling, has been validated in the rituximab era [11, 14] and in the setting of first-line stem cell transplantation [15]. Recent studies suggest that there may be an effect modification by chemotherapy regimen utilized in the first [16, 17] and the second line [18] setting.

The accumulating evidence regarding differential outcomes by biologic subtypes and the development of efficient methodology to assign individual patients to these are making their characterization in clinical trials and practice imperative. In the front-line setting, a completed intergroup study (C50303) is attempting to prospectively evaluate outcomes by molecular subtype and by chemotherapy regimen utilized. In the relapsed setting, BioCORAL identified differential activity of salvage regimens by disease subtype with R-DHAP performing better than R-ICE in the GCB but not the non-GCB or ABC cohorts. The future standard of care will undoubtedly incorporate assignment of DLBCL patients to molecular subtypes at diagnosis and salvage.

This is the first cooperative group study specifically targeted to the ABC subtype of DLBCL. We will register patients for the study who have been deemed to have non-GCB DLBCL as defined by IHC-based criteria (Hans algorithm). A secondary, correlative analysis will examine the subset of patients with ABC-DLBCL as determined by previously identified gene expression classifiers [14, 19] on paraffin-embedded tissue.

The BCR signaling pathway that is chronically active in ABC DLBCL has several members with well-recognized recurrent mutations. These include CD79, mutated in 20% of cases, and CARD11, mutated in ~10% [20]. Moreover, MYD88, an adaptor protein that mediates toll and interleukin (IL)-1 receptor signaling, is mutated in ~30% of cases of ABC DLBCL [21]. The presence of these mutations may affect response to ibrutinib therapy, as CD79 acts upstream of BTK, CARD11 is further downstream, and MYD88 interfaces with components of this pathway. In the phase II study reported recently, 5/7 patients with CD79 mutations and 4/5 patients with both CD79 and MYD88 mutations responded to ibrutinib, while none of the ABC patients with CARD11 mutations responded to the drug [22]. We hypothesize that these mutations will be significantly associated with outcomes in our study and we will collect archival tissue to assess for their presence. This trial will be the first to selectively target a molecular subtype of relapsed/refractory DLBCL and can potentially identify additional patient subgroups that are more likely to derive benefit from AutoHCT and ibrutinib independently. In this regard, it can make a major contribution to the treatment of patients with relapsed DLBCL and serve as a model for future trials.

1.2 Ibrutinib for ABC DLBCL

The B-Cell receptor (BCR) signaling pathway plays a prominent role in the pathobiology of ABC-subtype DLBCL [23]. Chronic active BCR signaling engages CARD11 to activate NF-kB, a key regulator of cell survival in this disease [24]. CARD11 is itself mutated in ~10% of ABC DLBCLs [24]. Bruton's tyrosine kinase (BTK) is upstream of CARD11 in the BCR signaling pathway [20]. A mutation in BTK leads to absence of B-cells in the developing organism, as established by the existence of the human genetic immunodeficiency disease X-linked agammaglobulinemia (XLA), and the mouse genetic immunodeficiency disease X-linked immunodeficiency [25]. Further upstream of BTK is CD79, which is mutated in more than 20% of ABC DLBCL tumors [23].

Ibrutinib is a first-in-class selective inhibitor of BTK with *in vitro* activity in ABC lymphoma cell lines [26] and clinical activity in ABC patients. In the phase I study involving 47 patients with lymphoid malignancies, ibrutinib was very well tolerated with minimal myelosuppression or liver function abnormalities and only isolated instances of grade 3 diarrhea and fatigue that were not clearly dose related. Notably, the incidence of grade 3 or 4 hematologic toxicity was only 8% in this heavily pretreated patient population. Despite the fact that most of the patients enrolled were refractory to prior therapy, a remarkable 51% overall response rate was observed with 3 of 8 (38%) patients with relapsed/refractory DLBCL responding [27, 28]. A relapsed, refractory DLBCL-specific phase II study of ibrutinib was recently reported [22]. This study enrolled 70 patients with a median of 3 (range 1-7) prior regimens, 23% of whom had relapsed

after autologous transplant. There was no excess hematological or other unexpected toxicity identified. In 25 reported cases with ABC subtype DLBCL, the response rate was 40% (8% CR, 32% PR) versus 5% in the patients with GCB. Progression-free survival was a median of 5.5 months in the ABC subgroup. This agent is active in relapsed and refractory ABC DLBCL as monotherapy. It is also tolerable and orally bioavailable on a once daily schedule, making it ideal for use during and following AutoHCT. We hypothesize that using ibrutinib in the setting of minimal disease burden will abrogate relapse and improve clinical outcomes.

1.3 Summary of Clinical Safety

Integrated safety data from a total of 1,523 subjects with B-cell malignancies treated with ibrutinib monotherapy in 17 studies that have completed primary analysis or final analysis included in the CSR as of the 31 July 2017 cutoff date for the current IB update in B-cell malignancies are summarized below.

The most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N = 1,523):

Most frequently reported TEAEs >10% [a]	Most frequently reported Grade 3 or 4 TEAEs >2% [a]	Most frequently reported Serious TEAEs >1% [b]
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Pyrexia
Cough	Anemia	Febrile neutropenia
Pyrexia	Hypertension	Sepsis
Anemia	Diarrhea	Cellulitis
Upper respiratory tract infection	Atrial fibrillation	Pleural effusion
Neutropenia	Fatigue	Dyspnoea
Oedema peripheral	Neutrophil count decreased	Urinary tract infection
Thrombocytopenia	Febrile Neutropenia	Lung infection
Muscle spasms	Hyponatraemia	Abdominal pain
Constipation	Hypokalaemia	Acute kidney injury
Arthralgia		Anemia
Vomiting		Respiratory failure
Decrease appetite		
Dyspnoea		
Headache		
Pneumonia		
Rash		
Hypertension		
Abdominal pain		
Back pain		
Contusion		
Dizziness		

[a] Source is Table 5 of IB (v11), [b] Source is Table 6 of IB (v11)

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

1.4 Selection of Primary Endpoint: 24-Month PFS

Since DLBCL is ultimately a curable disease, even in the relapsed/refractory setting, we designed this trial with a dichotomous primary endpoint that best captures the curative potential

of the proposed therapy. This assessment will occur 12 months following completion of ibrutinib or placebo therapy. Data from randomized studies in DLBCL suggest that the majority of the relapse events following AutoHCT occur in the first 24 months [7-9, 18]. Specifically in patients with relapsed DLBCL of the non-GCB subtype, Thieblemont et al suggest that over 80% of the relapses have occurred by 24 months [18]. Furthermore, a large population-based study has shown that 24-month event-free survival (defined-similarly to our definition of PFS in this trial) is very strongly associated with OS and is a robust endpoint for disease-related outcomes in DLBCL [29].

1.5 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 [30, 31].

2.0 OBJECTIVES

2.1 Primary objective

To evaluate the ability of ibrutinib to improve 24-month progression free survival (PFS) compared to placebo in patients with non-GCB DLBCL as determined by IHC.

2.2 Secondary objective(s)

2.2.1 To evaluate the ability of ibrutinib to improve overall survival (OS) compared to placebo.

2.2.2 To evaluate the ability of ibrutinib to improve progression free survival (PFS) compared to placebo.

2.2.3 To evaluate the ability of ibrutinib to improve post-transplant response rates compared to placebo.

2.2.4 To evaluate time to hematopoietic recovery in the two arms.

2.2.5 To evaluate the safety and tolerability of ibrutinib compared to placebo.

2.2.6 To evaluate the incidence of secondary malignancies in the two arms.

2.2.7 To evaluate immune reconstitution in the two arms.

2.3 Correlative science objective(s)

2.3.1 To assess whether pre-AutoHCT positive FDG-PET is associated with inferior 24-month PFS as well as PFS and OS.

2.3.2 To assess whether pre-AutoHCT FDG-PET results are differentially associated with 24-month PFS, PFS and OS in the ibrutinib versus placebo arms.

2.3.3 To evaluate the application of the Lugano criteria and change in quantitative measurements between pre-AutoHCT and post AutoHCT (e.g. delta SUV, %SUV decline and %MTV decline, and other available applicable quantitative measurements) to assess the association between changes in these variables and outcomes, such as PFS and OS.

2.3.4 To assess whether the GSTT1 null polymorphism is correlated with pulmonary toxicity after BCNU-containing conditioning regimens as part of autologous stem cell transplantation.

2.3.5 To assess whether other polymorphisms in the BCNU metabolism pathway or BCNU damage repair pathway(s) are associated with pulmonary toxicity after BCNU-containing conditioning regimens as part of autologous stem cell transplantation.

2.3.6 To evaluate whether any of the proposed DNA polymorphisms are associated with other toxicities.

2.3.7 To assess whether DLBCL subtype based on the Lymphoma Subtyping Test (LST) is associated with 24-month PFS, PFS, and OS with ibrutinib compared to placebo in patients treated on this protocol.

2.3.8 To assess whether activating mutations in the BCR pathway are associated with response to ibrutinib and with clinical outcomes in patients treated on this protocol.

2.3.9 To assess whether there are any phenotypic associations with IHC markers (particularly MYC protein expression level) and presence of these mutations.

2.3.10 To assess whether BCL2, MYC, and Ki67 expression by IHC affect clinical outcomes in patients treated on this protocol.

2.3.11 To assess whether translocations in MYC with or without BCL2 and BC6 have poor outcomes in patients treated on this protocol and whether ibrutinib modifies the prognosis.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 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:

NOTE that these guidelines are phrased in the negative; i.e., these are potential participants who should not be enrolled to the study.

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a “currently active” second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are free of disease for ≥ 3 years.
- Patients who cannot swallow oral formulations of ibrutinib.
- Significant non-hematologic toxicity from salvage therapy except for alopecia and fatigue.

3.2 Pre-Registration Eligibility Criteria (Step 0)

3.2.1 Central pathology review submission

Patients must have paraffin tissue from the diagnostic or relapse biopsy available to be submitted for central pathology review. This review is mandatory prior to registration to confirm eligibility and should be initiated as soon as possible.

3.3 Eligibility Criteria (Step 1)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

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).

___ **3.3.1 Documentation of Disease:**

Diagnosis of WHO diffuse large B-cell lymphoma, non-GCB by central review confirmation.

___ **3.3.2 Eligible for high-dose therapy and AutoHCT**

Patient must be deemed eligible to proceed with high-dose chemotherapy and autologous stem cell transplantation by local transplant center.

___ **3.3.3 Adequate organ function to proceed to transplant**

Patient must have adequate organ function to proceed to transplant as defined below:

___ **Cardiac:** New York Heart Association Class I or less. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or angina pain. Patients 60 years or older must have a left ventricular ejection fraction (LVEF) at rest ≥ 40% measured by echocardiogram or MUGA.

___ **Pulmonary:** DLCO (corrected or uncorrected for hemoglobin per institutional standards), FEV1, FVC ≥ 40% of predicted

___ **Hepatic:** Total Bilirubin ≤ 1.5 x upper limit of normal (ULN) unless isolated hyperbilirubinemia attributed to Gilbert's syndrome. AST and ALT ≤ 3 x upper limit of normal (ULN).

___ **Renal:** Creatinine ≤ 2.0 mg/dL OR creatinine clearance (calculated clearance permitted) ≥ 40 mL/min by Cockcroft-Gault formula.

___ PT/INR < 1.5 x ULN and PTT (aPTT) < 1.5 x ULN

___ **3.3.4 Prior Treatment**

___ Patient must have progressed or be refractory to prior anthracycline-containing chemotherapy (e.g. R-CHOP, DA-EPOCH-R, etc).

___ No more than 3 prior regimens for large cell component (e.g. one induction and two salvage therapies). Monoclonal antibody alone or involved field/involved site radiotherapy do not count as lines of therapy. Prior CART therapy is allowed and counts as one line of therapy.

___ Prior use of ibrutinib is allowed unless patient has had disease progression while receiving ibrutinib.

___ Patient must have chemosensitive disease as defined by at least a partial response to salvage therapy at their latest assessment.

___ No major surgery ≤ 7 days prior to registration and no minor surgery ≤ 3 days prior to registration (with the exception of intravenous access placement, e.g. Hickman or PICC).

___ **3.3.5 Not pregnant and not nursing,** because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative serum pregnancy test must be obtained within 14 days prior to registration.

Women of childbearing potential must use adequate contraception from study start to one month after the last dose of protocol therapy. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence. Men must practice complete abstinence or agree to use an adequate contraception method from study start to one month after the last dose of protocol therapy.

___ **3.3.6 Age ≥ 18 years**

___ **3.3.7 Concomitant medications**

___ Patients should not require chronic use of strong CYP3A inhibitors or strong CYP3A inducers (see Appendix II).

___ Patients should not require concurrent therapeutic doses of steroids (> 20 mg of prednisone/day or equivalent) unless they need them for the indications listed in Appendix II. Steroids should be discontinued for 14 days before starting protocol treatment.

___ **3.3.8 Intercurrent or Recent Illness**

___ HIV infected patients are eligible provided they meet all other eligibility criteria, and:

- There is no prior history of AIDS defining conditions other than historically low CD4+ T-cell count or B-cell lymphoma
- In the opinion of an expert in HIV disease, prospects for long-term survival are excellent were it not for the diagnosis of lymphoma
- Use of HIV protease inhibitors as part of the anti-HIV regimen OR as a pharmacologic booster is not allowed
- Zidovudine is not allowed
- Once daily combination pills for HIV containing a pharmacologic booster such as cobicistat are not allowed
- Patients with multi-drug resistant HIV are not eligible

Patients cannot have:

___ Active central nervous system or meningeal involvement by lymphoma. Patients with a history of CNS or meningeal involvement must be in a documented remission by CSF evaluation and contrast-enhanced MRI imaging for at least 91 days prior to registration.

___ Evidence of myelodysplasia or cytogenetic abnormality indicative of myelodysplasia on any bone marrow biopsy prior to initiation of therapy.

___ A known bleeding diathesis.

___ Requirement for warfarin or similar vitamin K antagonists. These drugs are prohibited 28 days prior to the first treatment and throughout the trial.

___ History of stroke or intracranial hemorrhage ≤ 6 months before treatment.

___ Currently active, clinically significant hepatic impairment (Child-Pugh class B or C according to the Child Pugh classification [see Appendix V]).

___ History of allergic reactions attributed to compounds of similar chemical or biologic composition to ibrutinib or other agents used in study.

___ Serologic status reflecting active hepatitis B or C infection. Patients that are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) prior to enrollment. (PCR positive patients will be excluded.)

___ **3.3.9 ECOG Performance Status must be ≤ 2**

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

IVR—MD, DO, or international equivalent;

NPIVR—advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);

AP—clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave; acting as a primary site contact, or with consenting privileges

Associate (A)—other clinical site staff involved in the conduct of NCI-sponsored trials; and

Associate Basic (AB)—individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

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

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

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Cancer Trials Support Unit Registration Procedures

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

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an Active CTEP status;
- Active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Site Registration Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password
- Click on Protocols in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, the select *Alliance* and protocol number A051301.
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU)

4.2.2 Requirements for A051301 Site Registration

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4.2.3 Checking Site Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.2.4 Submitting Regulatory Requirements

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

4.2.5 Delegation of Task Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.3 Patient Pre-Registration Requirements

- **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. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Central pathology review submission:** For all patients pre-registered to Alliance A051301, real time histopathology review is required. **FFPE tissue from the diagnostic or relapse biopsy for histopathology review is required for all patients at pre-registration.**

Pre-registration procedures: Patients who have 1) met pre-registration eligibility criteria and 2) been consented, will be pre-registered using the OPEN registration system per section 4.5. Once a patient has been pre-registered, the FFPE tissue should be sent to Cleveland Clinic **within 7 days**, along with the completed "Central Pathology Results Form." Failure to submit this form with the specimens will delay turnaround time for central review. The specimen will

be centrally reviewed to confirm study eligibility. See section 6.2 for specimen collection and submission details.

4.4 Patient Registration Requirements

- **Confirmation of eligibility by central review:** Within **5 business days of receipt of a suitable specimen sample** at Cleveland Clinic, sites will be notified via e-mail whether or not the patient is eligible based on the central pathology review. If a sample is deemed unsuitable after central pathology review, a request for an alternative sample will be made. The results section of the "Central Pathology Results Form" will be completed by the pathologist and laboratory performing the subtyping, scanned, and sent via e-mail to the responsible CRA listed on the form. After receiving the results form via e-mail, the institution must forward the form to the Alliance Patient Registration office at random01@mayo.edu in order to register the patient. Once the form is forwarded to the Alliance Patient Registration Office and the Registration and Randomization Eligibility Criteria have been met, the patient can be registered using the OPEN system per section 4.5. The same patient ID number obtained at pre-registration from the OPEN system should be used to register the patient. Retain the "Central Pathology Results Form" confirming eligibility for your records and to upload via Rave.
- **FDG-PET/CT** obtained during salvage therapy will be acquired at the time of study entry and will be centrally reviewed. Please note, this will not be a real time review to confirm eligibility. For more information see section 6.3 and section 14.1.

4.5 Patient Registration/Randomization 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://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

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. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

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 Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

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

To receive site reimbursement for specific tests and/or bio-specimen submissions, 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.

4.6 Registration to Correlative and Companion Studies

4.6.1 Registration to substudies described in section 14.0

There are two substudies within Alliance A051301. These correlative science studies **must be offered to all patients** enrolled on Alliance A051301 (although patients may opt to not participate). These substudies do not require separate IRB approval. The substudies included within Alliance A051301 are:

- "Pharmacogenetics of high-dose chemotherapy and treatment efficacy in relapsed/refractory DLBCL," Alliance A051301-PP1 (section 14.2)
- Biomarker studies in Alliance A051301 (A051301-ST1) (section 14.3)

If a patient answers "yes" to question #1 in the model consent, "I agree to have my blood specimen collected, and I agree that my specimen sample(s) and related information may be used for the blood study described above," they have consented to participate in the substudy described in section 14.2. The patient should be registered to Alliance A051301-PP1 at the same time they are registered to the treatment trial (A051301). Samples should be submitted per section 6.2.4.

If a patient answers "yes" to question #2 in the model consent, "I agree to have my tissue specimen collected, and I agree that my specimen sample(s) and related information may be used for the tissue study described above," they have consented to participate in the substudy described in section 14.3. The patient should be registered to Alliance A051301-ST1 at the same time they are registered to the treatment trial (A051301). Samples should be submitted per section 6.2.3.

4.7 Stratification and Grouping Factors

Patients will be assigned to one of the following groups at study entry: 1) Early safety assessment or 2) Double-blinded randomization.

Patients will be stratified at study entry by prior use of ibrutinib, type of transplant regimen planned (CBV vs. BEAM), and time to relapse (≤ 12 months or > 12 months). Time to relapse is calculated from day 1 of initial treatment (e.g. R-CHOP) to time of clinical relapse (by exam, imaging or pathology). Patients who never achieve a CR to front-line therapy are considered to be in the ≤ 12 months group.

4.8 Re-Registration at the time of progression

Progression is defined by the CT-based response criteria. Upon confirmation of progression, patients may elect to cross-over to treatment with ibrutinib as long as the following eligibility criteria are met:

ANC ≥ 1000/μL, platelets ≥ 30,000/μL
Serum creatinine ≤ 2.0 mg/dL OR
Calc. creatinine clearance ≥ 40 mL/min by Cockgroft-Gault
AST, ALT ≤ 2x ULN
Total bilirubin ≤1.5x ULN (except for patients with Gilbert's syndrome)

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 Alliance 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 Alliance coordinated protocols requires a "Registrar" role in the Alliance roster. Assignment of the "Registrar" role is managed through the Alliance Central Office via submission of a roster update form signed by the Principal Investigator of the member network.

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

5.0 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Note: Cycle 1 ends on AutoHCT day +29, and Cycle 2 begins with a Day 1 visit between AutoHCT day +30 and +60.

	Pre-registration assessment	Registration[#]	Cycle 1		Cycles 2-13	Clinical Follow up†	At PD, withdrawal, or removal £
			Day -6 or Day -7 of AutoHCT	Weekly until day +29*	Day 1 and Day 15 of Cycle 2. Day 1 of Cycles 3 through 13**		
Tests & Observations							
History and physical, Weight, PS		X	X		X	X	X
Height		X					
Pulse, Blood pressure		X					
ECG		X					
Adverse Event assessment		X	X	X	X	X	X
Patient medication diary			X(1)		X(1)		
Concomitant meds		X			X		X
Fatigue/ uniscale assessment		X(2)					
Laboratory Studies							
CBC, Differential, Platelets		X	X	X	X	X	X
Na, K, Cl, BUN, Serum creatinine, Glucose, Calcium		X	X	X	X	X	X
AST, ALT, Alk. Phos., Bili, Total protein, Albumin		X	X	X	X	X	X
Serum HCG		X(3)					
PFTs		X(4)			X(4)		
PT/INR, PTT (aPTT)		X					
Serum immunoglobulins, absolute B-cells, T-cell subsets		X(5)			X(5)	X(5)	
HBsAb, HBcAb, HBsAg, HCAb		X(6)					
ECHO or MUGA		X(7)					

Staging							
Central pathology review for eligibility	X(8)						
Tumor measurement		X			A	A	X
PET	X(9)	X(9)			B	B	X
CT/MRI chest/abd/pelvis		X(9)			C	C	X
BM biopsy					X(10)		
Correlative studies: For patients who consent to participate							
Tissue and blood samples	*X(12)*	*X(11)*					*X(12)*

\# Labs and observations may be obtained ≤ 30 days prior to visit unless otherwise noted.

* Labs to be obtained on Day +1, +8, +15, +22, and +29. If outpatient, these can be performed locally, provided the results are made available to the treating study health care provider within 24 hours.

** Treatment assessment on Day 1 and Day 15 of Cycle 2 and Day 1 of Cycles 3 through 13 can be performed outside the study/transplant center, provided the results are made available to the treating study investigator. There is a +/- 7 day window for every visit. For Cycle 2 only, labs and observations completed for the Cycle 1, Day +29 assessment can be used if obtained ≤ 7 days prior to Cycle 2, Day 1.

† **Clinical follow-up to be performed at the study/transplant center.** *For patients who complete all cycles 1-13*: clinical follow-up is at 18 and 24 months (+/- 1 month) from registration, then every 6 months (+/-1 month) until 5 years have elapsed from registration or until disease progression, whichever occurs first. Progression is defined by the CT-based response criteria. *For patients who discontinue study treatment in cycles 1-13 (for reasons other than progression or relapse)*: clinical follow-up is every 3 months (+/- 14 days) until 1 year from registration (e.g. at months 3, 6, 9, 12); these patients will continue protocol requirements per active treatment (for example, PET scan at 3 months, CT/MRI scans at 6, 12 months). Following 12 months, clinical follow-up is at 18 and 24 months (+/- 1 month) from registration, then every 6 months (+/- 1 month) until 5 years have elapsed from registration or until disease progression, whichever occurs first. Progression is defined by the CT-based response criteria.

£ After disease progression or start of alternative anticancer therapy, patients will be contacted approximately every 6 months by clinic visit or telephone to assess survival and the use of alternative anticancer therapy until death, withdrawal of consent, loss to follow up, study closure, or 5 years have elapsed from registration.

1 The Cycle 1 medication diary must begin when patient starts taking study drug on Day -6 or Day -7. For cycles 2-13, the diary must begin the day the patient starts taking study drug in Cycle 2. Medication diaries must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team (see Appendix III).

2 To be completed after registration and ≤ 45 days prior to treatment, see section 1.3 and Appendix I.

3 For women of childbearing potential (see section 3.3.3). Must be obtained within 14 days prior to registration.

4 Baseline PFTs with DLCO to be obtained within 84 days (12 weeks) prior to registration. Repeat PFTs with DLCO are strongly encouraged following AutoHCT at 3 months (+/- 1 month).

5 Quantitative immunoglobulin panels (IgG, IgM, IgA), absolute B-cell counts (CD19+), and T-cell subsets (CD3+, CD4+, CD8+) to be obtained at baseline and at 3, 6, 9, 12, 18, and 24 months (+/- 1 month) from registration.

6 Required for all patients prior to registration. Patients that are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) prior to enrollment. See section 3.3.8.

7 For patients 60 years or older (see section 3.3.3). To be obtained within 60 days prior to registration.

8 Paraffin tissue block from a diagnostic biopsy (obtained at diagnosis or relapse) should be submitted for central pathology review for subtype determination by gene expression profiling (see sections 4.3 and 6.2.2).

9 The FDG-PET/CT scan obtained during salvage therapy will be acquired at study entry and submitted for central review (see sections 4.4 and 6.3). Repeat FDG-PET/CT is not required for eligibility.
Baseline scans should include a whole body or limited whole body PET/CT or a PET and a diagnostic CT or MRI of the chest, abdomen, and pelvis documenting response to salvage therapy within 42 days of registration. The scans need to be submitted for subsequent central review (see section 6.3).

10 Bone marrow biopsy and aspirate performed for response assessment at 3 months only if positive prior to registration or if there is a clinical concern.
11 See section 6.2.4 for patients enrolled on substudy A051301-PP1.
12 See section 6.2.3 for patients enrolled on substudy A051301-ST1.
A Tumor measurements at 3, 6, 12, 18, and 24 months from registration.
B At 3 months (+/- 1 month) from registration, perform a whole body or limited whole body PET/CT or a PET with a diagnostic CT or MRI of the neck, chest, abdomen, pelvis. This scan is submitted for central review (see section 6.3). Patients who are receiving post-transplant radiation can have this assessment delayed by an additional month.
C At 6, 12, 18, and 24 months (+/- 1 month) from registration, perform a diagnostic CT or MRI of the neck, chest, abdomen, pelvis without a PET or a whole body or limited whole body PET/CT. The PET portion is not required by the study. These scans will be submitted for central review within 14 days of image acquisition (see section 6.3). Following 24 months, scans are performed at the discretion of the local investigator.

Crossover Phase (open label ibrutinib)

If a patient experiences disease progression and they are found to be receiving placebo, they may crossover to treatment with ibrutinib (see section 7.4). Progression is defined by the CT-based response criteria. Crossover patients will be re-registered to the study and followed per the study calendar below.

	Day 1 of each treatment cycle*	At end of treatment, PD, withdrawal, or removal £
Tests & Observations		
History and physical, Weight, PS	X	X
Adverse Event assessment	X	X
Patient medication diary	X(1)	
Concomitant meds	X	X
Laboratory Studies		
CBC, Differential, Platelets	X(2)	X
Na, K, Cl, BUN, Serum creatinine, Glucose, Calcium	X(2)	X
AST, ALT, Alk. Phos., Bili, Total protein, Albumin	X(2)	X
Staging		
Tumor measurement	A	X
CT/MRI chest/abd/pelvis	B	X

* Treatment assessment can be performed locally, provided the results are made available to the treating study healthcare provider within 24 hours. There is a +/- 7 day window for every visit.

£ Progression is defined by the CT-based response criteria. After patients complete 12 cycles of ibrutinib or discontinue crossover treatment for any reason, patients will be contacted approximately every 6 months by clinic visit or telephone to assess survival and the use of alternative anticancer therapy until death, withdrawal of consent, loss to follow up, study closure, or 5 years have elapsed from original study registration.

1 The medication diary must begin the day the patient starts taking ibrutinib in the crossover phase. Medication diaries must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team (see Appendix III).

2 Labs completed prior to crossover may be used for the Cycle 1 Day 1 tests if obtained ≤ 28 days prior to start of treatment.

A Tumor measurement will be performed every 3 months (+/- 1 month) during active therapy and at the discretion of the investigator thereafter. Tumor measurement on Day 1 of Cycle 1 is considered to be the tumor size at disease progression on placebo.

B Every 3 months during active therapy (+/- 1 month), perform a diagnostic CT or MRI of the chest, abdomen, pelvis without a PET or a whole body or limited whole body PET/CT. The PET portion is not required by the study. These scans do not need to be submitted for central review. Thereafter, scans are performed at the discretion of the investigator.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

6.1.2 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under Data Management > Rave Home and click to accept the invitation in the Tasks pane located in the upper right corner of the iMedidata screen. Site staff 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 eLearning link in the Tasks pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the Studies pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on

iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

6.1.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.1.4 Supporting documentation

This study requires supporting documentation for diagnosis and salvage response. At the time of disease progression, on study and off study visit, additional documentation is required. Supporting documentation will include pathology and radiology reports. These must be submitted at the following time points:

- Diagnostic biopsy report (initial diagnosis or relapse) submitted prior to registration.
- Radiology report from before and after last salvage assessment submitted prior to registration.
- Subsequent radiology reports and images will be submitted on study at 3, 6, and 12 months, and at 18 and 24 months of follow up. Radiology reports and images will also be submitted at the time of disease progression prior to crossover and for the off study assessment.
- Bone marrow biopsy report submitted prior to registration. Subsequent bone marrow biopsy report (if available) submitted at 3 months.
- Lab reports from Cycle 2 Day 1 assessment.

Additionally, the "Central Pathology Results Form" confirming eligibility must be uploaded via Rave on the Screening form.

6.2 Specimen collection and submission

The Alliance A051301 Correlative Science Manual (CSM) contains instructions for specimen collection, processing, and shipping. The manual can be found on the BioMS and CTSU websites. Questions regarding the CSM should be addressed to the contacts specified in the manual.

For all patients pre-registered to Alliance A051301: Real time histopathology review will be conducted using the paraffin tissue from a diagnostic biopsy (original diagnosis or relapse). **The submission of these samples for central histopathology review is required for all patients**

at pre-registration. Samples for central review should be submitted as soon as possible and within 7 days after pre-registration. See the table below and the CSM for specimen submission requirements.

For patients registered to substudies A051301-PP1 and A051301-ST1: All participating institutions must ask patients for their consent to participate in the correlative substudies, although patient participation is optional. Biomarker and pharmacogenetic studies will be performed. Rationale and methods for the scientific components of these studies are described in section 14.0. For patients who consent to participate, tissue and blood will be collected at the time points in the table below for these studies. **Please also see the study CSM for more instructions regarding specimen collection and submission.**

	Pre-registration	Registration	At Disease Progression or Relapse
Mandatory for all patients pre-registered to A051301:			
Original diagnostic stained slides OR 6 unstained slides (4-6 micron thickness) from archival paraffin diagnostic biopsy tissue[1]	X		
For patients registered to A051301-PP1, submit the following*:			
Whole Blood[2] (EDTA/lavender top)		1 x 10 mL	
For patients registered to A051301-ST1, submit the following:**			
Paraffin block/block alternative	X[3]		X[4,5]

1 Required for real-time central review to confirm eligibility. Biopsy can be acquired at the time of initial diagnosis or relapse. Submit original diagnostic stained slides: at least one H&E stained slide and stained slides for CD10, BCL6 and MUM1 used by the enrolling site for COO determination (including positive control stains) **OR** submit 6 unstained FFPE tissue sections (4-6 μm thickness) mounted onto positively charged slides. Slides should be freshly cut and packaged in a manner so that they do not break during shipment. If less than 6 slides are available, submit as many as possible.

2 Whole blood to be used for pharmacogenomics analyses described in section 14.2. This blood specimen should be collected prior to the initiation of protocol treatment. However, blood specimen collection may take place at a later time point while the patient is on study.

3 **Submission of a block is highly encouraged.** Absent the block, please see CSM for block alternative options.

4 Within 2 months of progression. Absent the block, please see CSM for block alternative options.

5 For patients randomized to the placebo arm who cross over to treatment with open-label ibrutinib, tissue should be submitted at both progression prior to crossover and progression following crossover.

* Collect and submit only from patients who answer "yes" to model consent question #1.

** Collect and submit only from patients who answer "yes" to model consent question #2.

6.3 Imaging submission

Images will be transmitted electronically from each participating site to the Imaging and Radiation Oncology Core Imaging Radiology Core (IROC) QA center at Ohio State University (IROC Ohio). The images will be reviewed by the Alliance Neuroradiology Core Review Group.

Images from the following time points must be submitted for central review:

- Pre-treatment assessment (prior to last line of salvage therapy)
- Baseline (following last line of salvage therapy)
- 3 months
- 6 months
- 12 months
- At 18 and 24 months of follow-up
- At time of disease progression prior to crossover (real-time review)
- Off-study assessment

Images will be collected digitally for central review (not necessarily in real time). Real-time central review of images is required upon local determination of disease progression prior to crossover. Real-time central review of these scans will be performed as described in section 6.3.2.

6.3.1 Imaging submission instructions

Complete data sets in digital DICOM format, along with Alliance Adjunctive Data Form (if applicable) and Alliance Image Measurement Form (if applicable), must be submitted to IROC Ohio **within 14 days of image acquisition**.

BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the scan is accepted by IROC. De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number and protocol number. The de-identified digital images may be temporarily burned to a CD or transferred to a PC based system.

Data should be transferred electronically (recommended) to IROC as follows:

Electronically

1) TRIAD based data transfer

   TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

   TRIAD Access Requirements:

   - Site physics staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account, and be registered as an AP, NPIVR or IVR. Please refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
   - To submit images, the site physics user must be on the site's affiliated rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role. RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

This process can be done in parallel to obtaining your CTEP-IAM account username and password and RCR registration.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

2) Web Transfer (http://upload.imagingcorelab.com)

Any PCs with internet access and web browser (e.g., Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to IROC. The standard Web Transfer information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

3) FTP Transfer

Any FTP software can be used to initiate access to the secure FTP Server of IROC. The standard FTP access information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

Mail/CD Shipment

Only if electronic data transfer approaches cannot be achieved, the de-identified images in digital DICOM format can be burned to a CD and mailed to IROC Ohio. Submit only one patient's images per CD, with the patient's Alliance ID number, study type, date of scans, and name of submitting institution.

Submit these data to:

IROC Ohio
Attn: Alliance Trial A051301
The Ohio State University
Wright Center of Innovation
395 W. 12th Avenue, Room 428
Columbus, Ohio, 43210
Tel: [redacted]
Fax: [redacted]

Once the imaging data submission is done, send an e-mail to IROC Ohio at the specific trial email (alliance051301@irocohio.org) to inform that the study has been submitted from the institution. Please include the basic information of submitted data sets as follows:

1) Alliance patient ID number
2) Scan time point (i.e., baseline)
3) Date of scans
4) Institution name

IROC will acknowledge receipt of the imaging data via email confirmation to the institution within 1 business day of receipt, and will notify the institution and Alliance imaging committee of the quality check report within 3 business days.

6.3.2 Real-time central imaging review

A real-time imaging central review will be performed at the time of disease progression prior to crossover.

Participating site needs to notify IROC Ohio of local radiology assessment at the time of site determination of **PD,** and all imaging studies will be centrally reviewed to evaluate for efficacy on a per time point basis and to confirm the presence of **PD.**

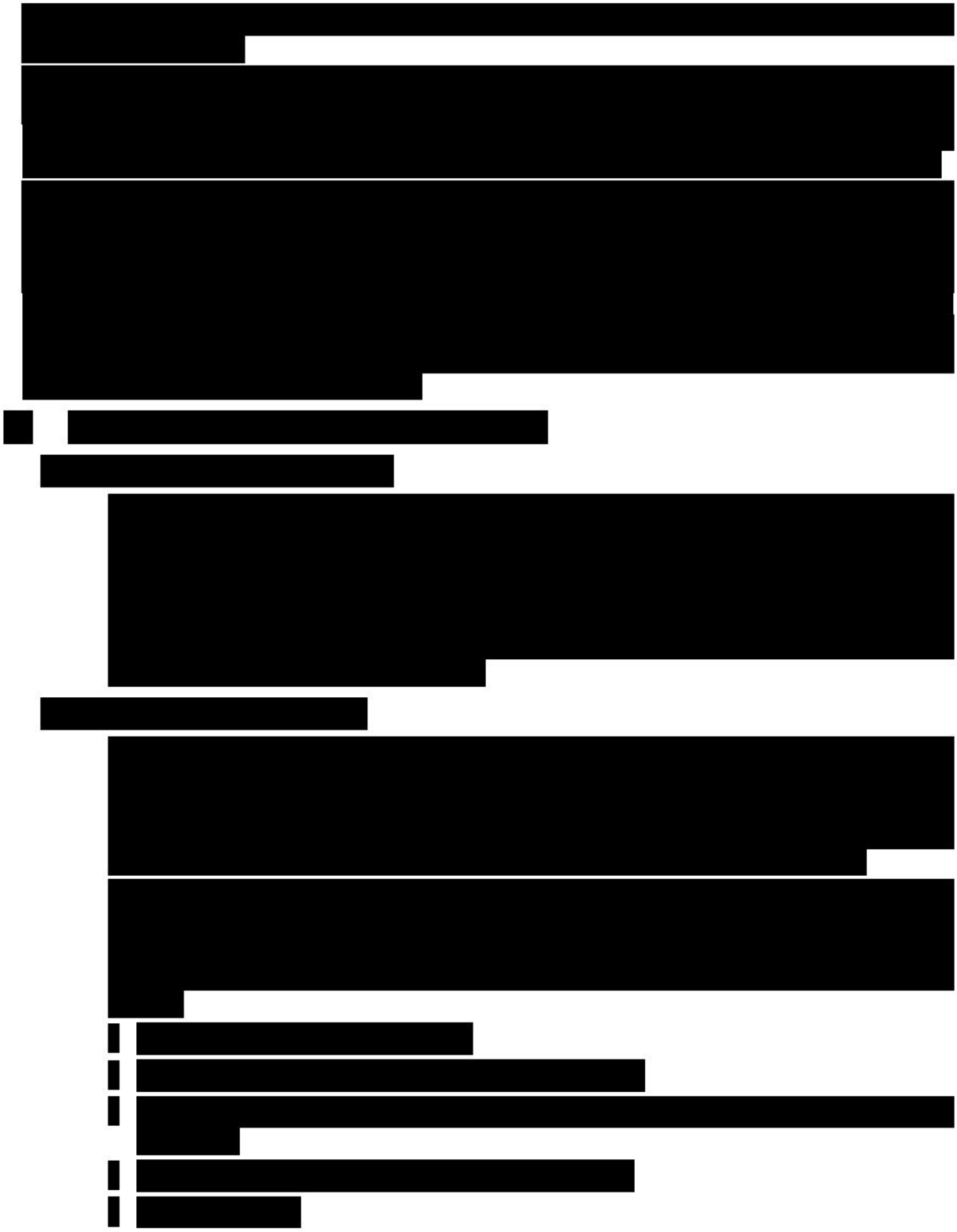
Complete the "Alliance A051301 Central Review Form – Progression" and submit to IROC Ohio along with the electronic submission of the images. For Alliance members, the form may be found on the A051301 study page on the Alliance website under the "Supplemental Materials" tab. For non-Alliance institutions, the form can be found under the "LPO Documents" tab on the CTSU A051301 study page (www.ctsu.org).

IROC Ohio will contact the A051301 central review panel **within 24 hours (except weekends and holidays) of images being received** for scheduling a real-time remote review. IROC notifies both the participating site and Alliance of the central review results **within 24 hours after receiving the results from the central review panel**. The overall turn-around time between imaging data receipt and central review results notification is **within 24-72 hours** after the imaging data receipt **(except weekends and holidays)**.

Central review results will be reported back to the site PI for further evaluation and determination of patient status.

The final treatment decision is determined by the central review. If progressive disease is the final determination by the central review adjudication of the results, blinded treatment will be discontinued and the patient will be unblinded. If patient is found to be on placebo, they may elect to crossover to open-label ibrutinib.

7.0 TREATMENT PLAN/INTERVENTION



[redacted]

7.4 Crossover at Disease Progression

Progression is defined as PD by the CT-based response criteria. At the time of documented disease progression as determined by central imaging review, patients may be unblinded (see section 6.3). Patients found to be receiving placebo will be allowed to crossover to ibrutinib 560 mg daily as long as the following eligibility criteria are met:

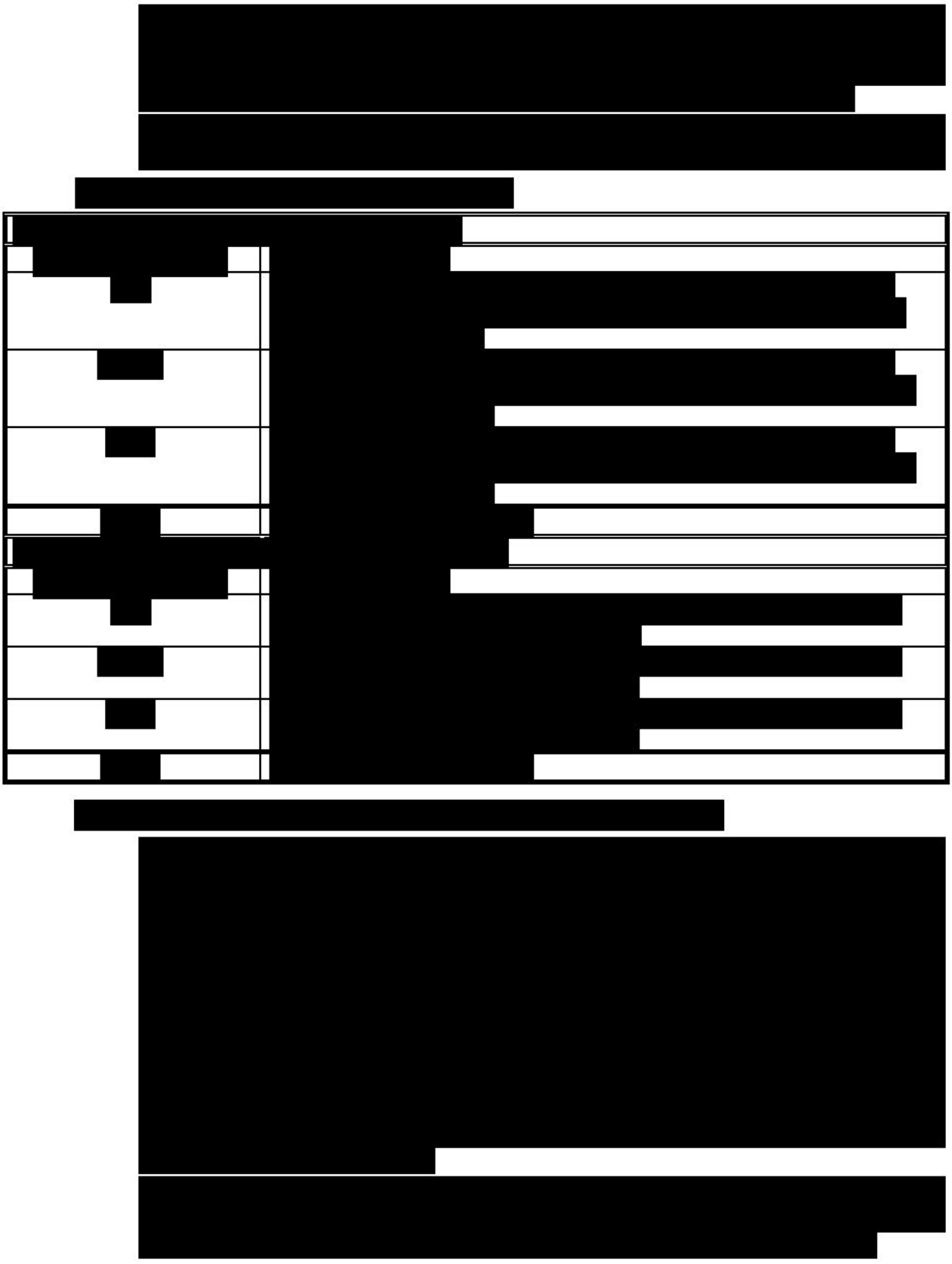
ANC ≥ 1000/μL, platelets ≥ 30,000/μL
Serum creatinine ≤ 2.0 mg/dL OR
Calc. creatinine clearance ≥ 40 mL/min by Cockcroft-Gault
AST, ALT ≤ 2 x ULN
Total bilirubin ≤ 1.5 x ULN (except for patients with Gilbert's syndrome)

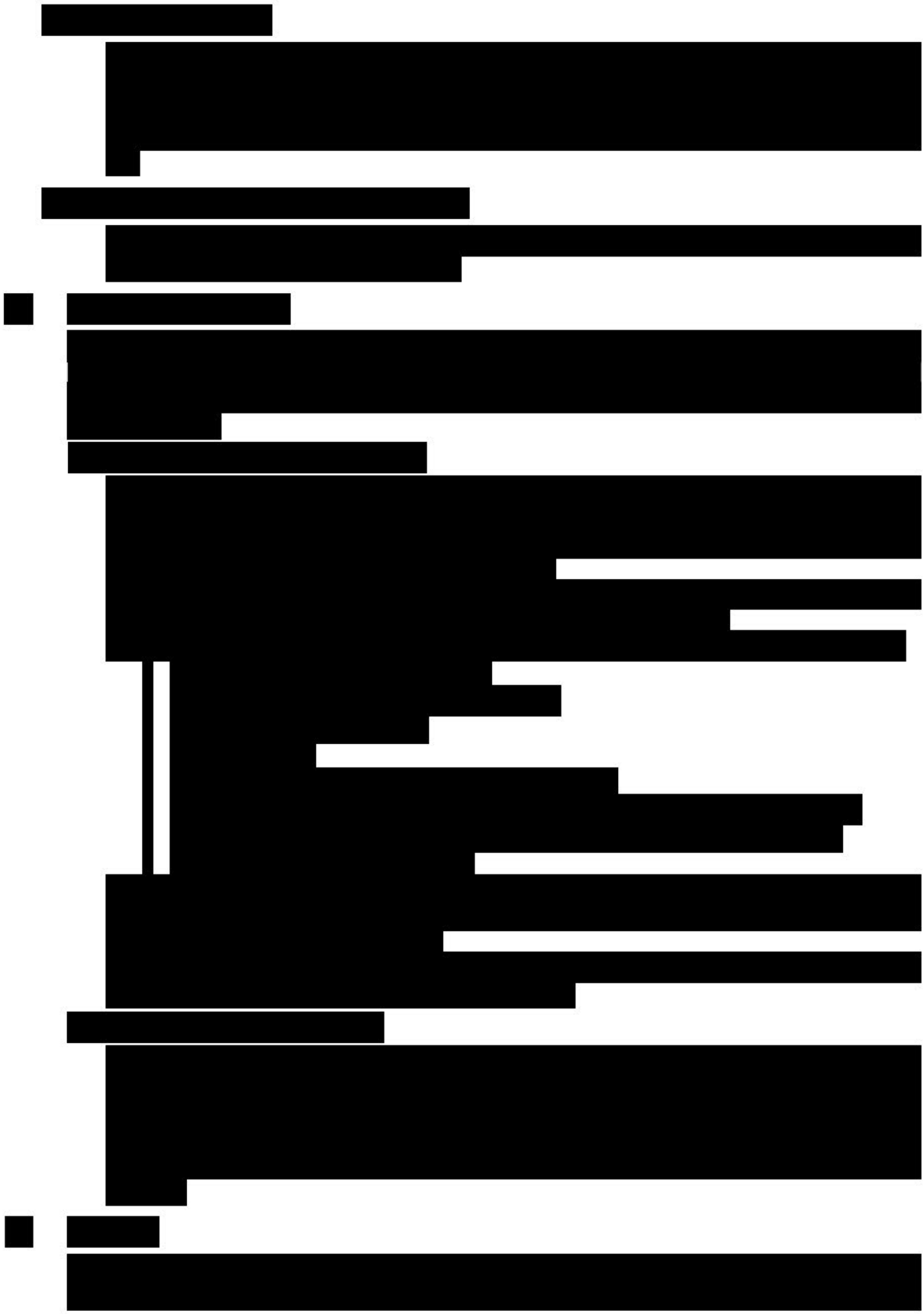
Patients should be re-registered to the crossover portion of the study within 4 weeks of documented progression per section 4.8. Once the patient has been re-registered, the initial shipment of ibrutinib will arrive within 7-10 days. Patients will begin therapy on 28-day cycles until subsequent disease progression or 12 cycles of therapy, whichever occurs first. A 7-day break without taking drug is also allowed up to two times for reasons other than dose adjustment or modifications (i.e. "drug holidays"). Documentation to justify these interruptions should be maintained in the study record. See section 8.0 for ancillary/concomitant therapy and dose modifications.

8.0 Dose and Treatment Modifications, Unblinding

[redacted]

depending upon the type of surgery and the risk of bleeding (see Section 10.2). Patients with





[redacted]

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. However, CTCAE v5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. The CTCAE is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine adverse event reporting

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 according to the study calendar in section 5.0. For this trial, Adverse Event Form: Solicited is used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Nausea	Gastrointestinal disorders
Vomiting	Gastrointestinal disorders
Diarrhea	Gastrointestinal disorders
Constipation	Gastrointestinal disorders
Rash maculo-papular	Skin and subcutaneous tissue disorders
Fatigue	General disorders and administration site conditions
Fever	General disorders and administration site conditions
Anorexia	Metabolism and nutrition disorders
Dyspnea	Respiratory, thoracic and mediastinal disorders
Cough	Respiratory, thoracic and mediastinal disorders

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center.

***Cycle 1: Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs). Only unexpected AEs relative to stem cell transplant will be reported.**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

***Cycles 2-13: Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible	a	a	a, b	a, b	a, b
Probable	a	a	a, b	a, b	a, b
Definite	a	a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Investigational Drug Branch (IDB), the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. 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. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) accessed via https://eapps-ctep.nci.nih.gov/ctepaers/.

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

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.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.,* radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

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

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

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

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

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

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Alliance A051301 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.
- Hematosuppression ≤ grade 3-4 resulting in hospitalization do not require CTEP-AERS; however these events should still be reported as routine adverse events via CDUS. All other grade 3 or 4 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.
- All suspected and confirmed cases of fungal infections should be reported to CTEP within 24 hours.
- All new malignancies must be reported via 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/acute myelogenous leukemia, 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 or 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.

  Secondary Malignancy: A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. CTEP requires

all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE to be reported via CTEP-AERS. Three options are available to describe the event:

1) Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
2) Myelodysplastic syndrome (MDS)
3) Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

- Treatment expected adverse events include those listed in section 9.4, section 10.0, and in the package inserts of the commercially available agents.
- CTEP-AERS reports should be submitted electronically.
- **Pregnancy:** Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

  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.

  A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

  When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and submitted at the time the pregnancy is known and within 30 days of becoming aware of the outcome, along with any additional medical information (form is available on the CTEP website at http://ctep.cancer.gov/). The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

9.3.2 Adverse Events of Special Interest

Specific adverse events or groups of adverse events will be followed as part of standard safety monitoring activities at the National Cancer Institute-Division of Cancer Treatment and Diagnosis. These events will be reported to the sponsor **via CTEP-AERS** within 24 hours of awareness following the procedures described for SAEs and 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.** These events are:

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*

9.4 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Ibrutinib (NSC # 748645, IND# 117241)

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 CTEP-AERS (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 2086 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 2.7, November 16, 2021[1]

Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 5.0 Term) [n= 2086]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders - Other (leukostasis)	
	Febrile neutropenia		
		Leukocytosis	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Atrial flutter	
		Heart failure	
		Ventricular arrhythmia	
		Ventricular fibrillation	
		Ventricular tachycardia	
EYE DISORDERS			
	Blurred vision		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Mucositis oral		
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			

Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 5.0 Term) [n= 2086]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Edema limbs		
	Fatigue		***Fatigue (Gr 3)***
	Fever		
		Sudden death NOS	
HEPATOBILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
	Infection[3]		***Infection[3] (Gr 3)***
		Infections and infestations - Other (bronchopulmonary and central nervous system infections)[4]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		
INVESTIGATIONS			
	Lymphocyte count increased[2]		
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia Dehydration		
		Hyperuricemia	
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Muscle cramp		
	Myalgia		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (benign neoplasm of skin)[5]		
		Treatment related secondary malignancy[5]	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		
		Peripheral sensory neuropathy	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		

Adverse Events with Possible Relationship to Ibrutinib (PCI-32765) (CTCAE 5.0 Term) [n= 2086]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Pneumonitis[6]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Skin and subcutaneous tissue disorders - Other (angioedema)[7]	
	Skin and subcutaneous tissue disorders - Other (rash)[8]		***Skin and subcutaneous tissue disorders - Other (rash)[8] (Gr 3)***
		Stevens-Johnson syndrome	
VASCULAR DISORDERS			
	Hypertension		
		Hypotension	
	Vascular disorders - Other (hemorrhage)[9]		

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

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

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

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

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

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

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

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

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

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

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

CARDIAC DISORDERS - Atrioventricular block complete; Atrioventricular block first degree; Cardiac disorders - Other (bundle branch block left); Cardiac disorders - Other (extrasystoles); Chest pain - cardiac; Myocardial infarction; Palpitations; Pericardial effusion; Pericarditis; Sinus bradycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear pain
EYE DISORDERS - Dry eye; Eye disorders - Other (eye discharge); Eye disorders - Other (macular edema); Eye disorders - Other (ocular hyperemia); Eye disorders - Other (retinal hemorrhage); Eye pain; Floaters; Glaucoma; Keratitis; Periorbital edema; Photophobia; Vision decreased; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Cheilitis; Colitis; Dyspepsia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gluteal intramuscular bleed); Gastrointestinal disorders - Other (irritable bowel syndrome); Gastrointestinal disorders - Other (tongue discoloration); Oral dysesthesia; Oral pain; Pancreatitis; Periodontal disease; Small intestinal obstruction; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (early satiety); General disorders and administration site conditions - Other (multiple organ dysfunction syndrome); General disorders and administration site conditions - Other (sensation of foreign body); General disorders and administration site conditions - Other (temperature intolerance); Generalized edema; Injection site reaction; Localized edema; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)
INFECTIONS AND INFESTATIONS - Conjunctivitis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Infusion related reaction; Injury, poisoning and procedural complications - Other (excoriation)
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (cardiac murmur); Investigations - Other (increase CRP); Lymphocyte count decreased; Weight gain; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (cachexia); Metabolism and nutrition disorders - Other (hypoproteinaemia); 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 (PML); Nervous system disorders - Other (parosmia); 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); Urine discoloration; Urinary frequency; Urinary retention
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 (alveolitis allergic); 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.

10.0 DRUG INFORMATION

10.1 General Considerations:

The use of individual institution guidelines in the preparation, administration, and timing of the chemotherapeutic agents BCNU (carmustine), etoposide, cytarabine, cyclophosphamide, and melphalan is allowed.

10.2 Ibrutinib (NSC #748645, [redacted])

Availability

Ibrutinib (NSC 748645) and matching placebo will be provided free of charge by Pharmacyclics, Inc. and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Ibrutinib (NSC 748645) is supplied as hard gelatin capsules containing micronized ibrutinib and the following excipients: microcrystalline cellulose; croscarmellose sodium; sodium lauryl sulfate; may contain magnesium stearate. Capsules are manufactured as 140mg in a size 0, gray, hard gelatin capsule. The placebo capsules are identical in size and shape, but do not contain ibrutinib. Capsules are packaged in high-density polyethylene (HDPE) bottles with an induction seal and a child resistant screw top cap. Each bottle contains 120 capsules. Ibrutinib and matching placebo capsules are to be dispensed in their original containers.

Each blinded or open-label, patient-specific bottle will be labeled with:

- The protocol number (i.e., ***A051301***)
- The bottle number (i.e., "Bottle 1 of 2", "Bottle 2 of 2", etc.)
- The number of tablets (i.e,"120 capsules")
- The patient ID number (e.g., "999999")
- The patient initials (i.e., **L**ast initial, **F**irst initial, **M**iddle initial [e.g., "L, FM"])
- The agent identification (i.e., "Ibrutinib 140 mg" or "Ibrutinib 140 mg or Placebo")
- A blank line for the pharmacist to enter the patient's name
- Administration instructions (i.e., "Take __ capsules daily.")
- Storage instructions (i.e., "Store at Controlled Room Temperature between 15° and 25°C.")
- Emergency contact instructions
- A Julian date

Julian Dating

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2014 = 14, 2015 = 15) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2014 would have a Julian date of '14001' and a bottle labeled and shipped on December 31, 2014 would have a Julian date of '14365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both veliparib and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind. The Julian Date – Order number (e.g., 14352-0003) from the patient-specific label must be used as the Lot number on the NCI DARF.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (240) 276-6575 Monday through Friday between 8:30am and 4:30pm Eastern Time. You may also contact the PMB via e-mail at PMBAfterHours@mail.nih.gov.

Initial Supply/Starter Supplies

Agent Orders:

SAFETY RUN-IN (OPEN-LABEL)

No open-label starter supplies will be available for this study. Open-label, patient specific clinical supplies will be sent to the registering investigator at the time of registration to the safety run-in and should arrive within approximately 7 to 10 days. This registration will be performed by the Alliance Statistical Center. Once a patient has been registered, the Alliance Statistical Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the Alliance Statistical Center the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day. Shipments within the United States will be sent by FedEx Ground and shipments to Canada (if participating) will be sent by FedEx (generally one to two day delivery. Shipments to United States sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the Alliance Statistical Center at the time the patient is registered.

The initial request will be for 3 bottles of ibrutinib 140 mg [this supply will cover the Conditioning Regimen plus the first 2 cycles of treatment]. Approximately 2 weeks after cycle 3 begins (2 weeks before needed), sites may reorder an additional 2 bottles [a 2 cycle (8 week) supply at a dose of 4 capsules given once daily] of ibrutinib 140 mg using the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an “active” account status and a “current” password. The assigned patient ID number (e.g., "999999") and the patient initials (e.g., "L,FM") must be entered in the "Patient or Special Code" field. A separate order is required for each patient ID number (e.g., "999999") being ordered. All drug orders will be shipped directly to the physician responsible for treating the patient.

BLINDED PHASE

No blinded starter supplies will be available for this study. Blinded, patient specific clinical supplies will be sent to the registering investigator at the time of randomization and should arrive within approximately 7 to 10 days. This randomization will be performed by the Alliance Statistical Center. The assigned Alliance patient ID number must be recorded by the registering institution for proper bottle dispersion. Once a patient has been registered, the Alliance Statistical Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the Alliance Statistical Center the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day. Shipments within the United States will be sent by FedEx Ground (up to 5 business days for delivery) and shipments to Canada (if participating) will be sent by FedEx (generally one to two day delivery). Shipments to United States sites can be expedited by the provision of an express courier account name and number to the Alliance Statistical Center at the time the patient is randomized. Please note that additional processing time is required for QA/QC checks on patient-specific/blinded orders and next day delivery is not available.

The initial request will be for 3 bottles of ibrutinib 140 mg or placebo [this supply will cover the Conditioning Regimen plus the first 2 cycles of treatment]. Approximately 2 weeks after cycle 3 begins (2 weeks before needed), sites may reorder an additional 2 bottles [a 2 cycle (8 week) supply at a dose of 4 capsules given once daily] of ibrutinib 140 mg or placebo using the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). (See Safety Run-In section for information on

drug orders and access to OAOP). All drug orders will be shipped directly to the physician responsible for treating the patient.

UNBLINDED CROSSOVER PHASE (OPEN-LABEL)

NOTE: Patients will not be able to obtain unblinded supplies until the patient has been unblinded (at progression) by following the unblinding procedures in section 8.3 AND a clinical drug request has been transmitted to the PMB. The patient ID number will NOT change for the cross-over portion of the study.

No open-label starter supplies will be available for this study. Open-label, patient specific clinical supplies will be sent to the registering investigator at the time of re-registration and should arrive within approximately 7 to 10 days. This re-registration will be performed by the Alliance Statistical Center. Once a patient has been re-registered, the Alliance Statistical Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the Alliance Statistical Center the day the patient is re-registered and will be processed by the PMB the next business day and shipped the following business day. Shipments within the United States will be sent by FedEx Ground and shipments to Canada (if participating) will be sent by FedEx (generally one to two day delivery. Shipments to United States sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the Alliance Statistical Center at the time the patient is re-registered.

The initial request will be for 2 bottles of ibrutinib 140 mg [a 2 cycle (8 week) supply at a dose of 4 capsules given once daily]. Approximately 2 weeks after cycle 3 begins (2 weeks before needed), sites may reorder an additional 2 bottles [a 2 cycle (8 week) supply at a dose of 4 capsules given once daily] of ibrutinib 140 mg using the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). (See Safety Run-In section for information on drug orders and access to OAOP). The patient may receive up to 12 cycles of open-label ibrutinib therapy. All drug orders will be shipped directly to the physician responsible for treating the patient.

Drug Transfers

Tablets MAY NOT be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 240-276-7893) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., "99999"') and the patient initials (e.g., "L, FM") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "A051301").

Drug Returns

When it is necessary to return **undispensed** study drug (e.g., sealed or partial bottles remaining when a patient permanently discontinues protocol treatment, expired bottles recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., "99999") and the patient initials (e.g., "L, FM") should be entered in the "Lot Number" field.

Drug Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI

Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "99999") and each Phase (Blinded and Unblinded Crossover) on this protocol. NOTE: The Julian Date – Order number combination found in the upper right-hand portion of the patient-specific label must be used as the Lot Number. This number will be used in the event of a stock recovery or recall of the investigational agent.

Investigator Brochure Availability

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

Useful Links and Contacts

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

Storage and Stability

Ibrutinib Hard Gelatin Capsules should be stored at 15 – 25°C. Shelf life surveillance of the intact bottles is ongoing.

Administration

Ibrutinib is to be taken orally, with 8 ounces (approximately 240 mL) of water. The capsules are to be swallowed intact and patients should not attempt to open capsules or dissolve them in water. Doses are to be taken at about the same time each day. If a dose is missed, it should be made up as soon as possible on the same day, with a return to the normal schedule the following day. Extra doses should **not** be taken to make up for missed doses.

Subjects who require surgical intervention or an invasive procedure while receiving ibrutinib/placebo should follow the administration guidelines below:

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

- For minor procedures (such as a central line placement, skin or needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis), ibrutinib/placebo 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/placebo, it is not necessary to hold ibrutinib/placebo for these procedures.

Drug Interactions

CYP3A Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong CYP3A4 or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Refer to section 8.1 if a strong or moderate CYP3A inhibitor must be used. Avoid concomitant use of strong CYP3A inducers. Consider alternative agents with less CYP3A induction.

For the most comprehensive effect of CYP3A inhibitors or inducers on ibrutinib exposure, please refer to the current version of the IB. See Appendix II for more information.

Mesna

Mesna possesses a sulfhydryl group that can react with ibrutinib. Avoid mesna dosing 6 hours before and after ibrutinib/placebo dosing due to potential interaction with ibrutinib.

Adverse Events

For a comprehensive adverse events and potential risks lists (CAEPR), please see section 9.4.

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.

Initially, subjects were excluded from participation in specific ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib unless specified in the protocol. Supplements such as fish oil and vitamin E preparations should be avoided. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Use of ibrutinib in patients requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. See Section 8.1 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding. Patients with congenital bleeding diathesis have not been studied.

Atrial fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor subjects clinically for atrial fibrillation. Subjects who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 8.2).

Cytopenias

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

Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged, follow the protocol dose modifications (see section 8.2).

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (see Section 8.1). Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. If observed, enter data in the corresponding eCRF.

Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

Tumor Lysis Syndrome

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

Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines as needed (see Section 8.2).

Non-melanoma Skin Cancer

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

Hypertension

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

Nursing Guidelines

There are numerous drug to drug interactions. Record all of patient's medications including OTC, and herbal use. Avoid concomitant use with agents as listed in Appendix II.

Patients should be instructed to avoid eating grapefruit (including juice) and Seville oranges while on ibrutinib.

Peripheral edema is common. Instruct patients to report this to the study team.

Gastrointestinal side effects are common (diarrhea, nausea, constipation, abdominal pain, vomiting, etc). Treat symptomatically and monitor for effectiveness of intervention.

Monitor CBC w/diff. Instruct patients in energy conserving lifestyle (anemia) and to report any unusual bruising or bleeding and/or signs or symptoms of infection to study team.

Arthralgias, myalgias, and muscle spasm can be seen. Treat symptomatically and monitor for effectiveness.

Monitor renal function/uric acid levels, especially in patients who may be experiencing dehydration.

Respiratory symptoms may include, cough, SOB, and URI. Instruct patients to report these symptoms to the study team.

Rarely patients can experience secondary skin cancers. Instruct patients to report any new skin lesions to the study team.

Rash can be seen. Instruct patient to report to study team.

10.3 BCNU (Carmustine, NSC# 409962)

Procurement

Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Carmustine is supplied as a lyophilized powder containing no preservatives. Please refer to the FDA-approved package insert for complete prescribing information.

Storage and Stability

Unopened vials are stable under refrigeration until the labeled expiration date on the commercially available product. BCNU has a low melting point requiring refrigeration at all times prior to reconstitution. Do not use if an oil film is present at the bottom of vial.

Preparation

Due to its water insolubility, it is to be reconstituted with the diluent provided (3 mL of absolute ethanol) and then with either 27 mL or 17 mL of sterile water for injection to provide a resulting concentration of 3.3 mg/mL or 5 mg/mL, respectively. After reconstitution, carmustine should be further diluted with 500 mL 5% Dextrose or normal saline and will be stable for 8 hours at room temperature. It is recommended to use PVC-free bags and tubing.

Administration

Carmustine should be given over 2 hours or per institutional guidelines.

Pharmacokinetics

Carmustine is rapidly metabolized in the liver and is rapidly degraded to active metabolites. Sixty to 70% is excreted in the urine in 96 hours and 10% as respiratory CO_2. Because of the high lipid solubility, it crosses the blood-brain barrier readily.

Adverse Events

The most frequent and most serious toxicity of BCNU is delayed myelosuppression. Pulmonary infiltrates and/or fibrosis, dry cough and difficulty breathing have been reported. Cases of fatal pulmonary toxicity with BCNU have been reported. Nausea and vomiting are very common. A reversible hepatic toxicity is demonstrated by elevated SGOT, alkaline phosphatase and bilirubin.

Renal abnormalities consisting of progressive azotemia, decrease in kidney size and renal failure have been reported.

Thrombophlebitis and local ulceration occur if extravasation occurs. Venous pain and flushing during injection and a brownish discoloration of skin on contact have also occurred.

Rapid infusion may produce intensive flushing. Neuroretinitis has been reported. The occurrence of acute leukemia and bone marrow dysplasia have been reported in patients following long-term nitrosourea therapy. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

Nursing Guidelines

Nausea and vomiting appears within 2 hours of dosing, usually lasting 4-6 hours and can be dose limiting. Premedicate with antiemetics and assess for response.

Drug is an irritant – avoid skin contact. Irritation at the injection site or along the vein is common. May need to apply an ice pack above the injection site and decrease the infusion rate.

Administer slowly to avoid severe local reaction, dizziness, and hypotension.

Monitor hepatic, renal function tests.

Monitor CBC. Due to delayed and cumulative myelosuppression (4-6 weeks), monitor CBC for at least 6 weeks after a dose.

Rapid IV infusion may cause intense flushing of the skin and suffusion of the conjunctiva within 2 hours, lasting approximately 4 hours. Neuroretinitis has been seen.

Instruct patient to avoid the use of cimetidine as this may increase the severity of myelosuppression.

Monitor phenytoin levels closely, as carmustine may decrease phenytoin levels.

Pulmonary toxicity (interstitial fibrosis) is noted at higher dose levels and may present as late as 3 years after dosing. Instruct patient to report and cough, SOB, dyspnea, or chest pain to the health care team immediately.

10.4 Cyclophosphamide (NSC# 26271)

Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available as a powder for reconstitution in 100 mg, 200 mg, 500 mg, 1 gram, and 2 gram vials. Please refer to the FDA-approved package insert for cyclophosphamide for product information, extensive preparation instructions, and a comprehensive list of adverse events.

Storage and Stability

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

Preparation

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

Administration

The total dose of cyclophosphamide will be administered by IV. Supportive hydration should also be given per institutional guidelines. MESNA should be administered with cyclophosphamide as per institutional guidelines.

Drug Interactions

Cyclophosphamide undergoes metabolic activation via cytochrome P450 3A4 in the liver and may potentially interact with any drug affecting the same isoenzyme. Inhibitors of 3A4 (e.g., itraconazole) could theoretically inhibit activation and inducers of 3A4 (e.g., phenytoin) could theoretically enhance activation of cyclophosphamide to active alkylating species. For the most part, such interactions have not yet been documented clinically.

Mesna possesses a sulfhydryl group that can react with ibrutinib. Avoid mesna dosing 6 hours before and after ibrutinib/placebo dosing due to potential interaction with ibrutinib.

Pharmacokinetics

Cyclophosphamide is metabolized hepatically via CYP3A4 to its active metabolite and acreolin (responsible for hemorrhagic cystitis). Strong CYP3A4 inhibitors or inducers should be avoided during administration of cyclophosphamide.

Adverse Events

Myelosuppression, hemorrhagic cystitis (patients must be well-hydrated before, during, and after treatment and have adequate renal function). Syndrome of inappropriate antidiuretic hormone (SIADH), fatigue, alopecia, anorexia, nausea, vomiting, hyperuricemia, azospermia, amenorrhea, cardiotoxicity (myocardial necrosis) has been seen with transplant-type doses.

Nursing Guidelines

Myelosuppression is common. Monitor CBC including platelets. Instruct patient on signs/symptoms of infection and to inform health care team of any unusual bruising, or signs of bleeding.

Instruct patient to drink 2-3 liters of fluid per day for 2-3 days following treatment and to void frequently, not greater than every three hours to facilitate keeping the bladder clear of drug.

Instruct patient to report any urinary urgency, frequency, dysuria, or hematuria. Administer mesna with high dose cytoxan to prevent hemorrhagic cystitis. It may be necessary to catheterize and provide constant bladder irrigation.

Advise patient of possible strong metallic taste associated with Cytoxan and suggest hard candy with a strong flavor (cinnamon, peppermint) to alleviate it.

Administer antiemetics as necessary to minimize nausea and vomiting, which usually occurs 6-8 hours after administration.

Report and record any complaint of lightheadedness, facial “heat sensation,” diaphoresis during administration.

Use of an ice cap may be helpful in preventing or limiting alopecia.

Corticosteroids, phenothiazine, imipramine, vitamin A succinylcholine, digoxin, thiazide diuretics, warfarin and allopurinol may inhibit Cytoxan metabolism and modify its' effect. They may also increase bone marrow suppression.

Advise female patients of possible menstrual changes or amenorrhea.

Patients on anticoagulant therapy should have INR levels carefully monitored as cytoxan increases their effect.

Monitor electrolytes and for signs/symptoms of SIADH and tumor lysis syndrome.

Monitor digoxin levels closely as cytoxan may decrease these levels.

Cytoxan may potentiate doxorubicin-induced cardiomyopathy. Instruct patient to report any chest pain.

10.5 Etoposide (NSC# 141540)

Procurement

Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Etoposide is commercially available as a solution for injection in 5 mL, 7.5 mL, 25 mL, and 50 mL vials containing 20 mg/mL. Please refer to the FDA-approved package insert for etoposide for product information, extensive preparation instructions, and a comprehensive list of adverse events.

Storage and Stability

Intact vials of etoposide for injection should be stored at room temperature and protected from light.

Preparation

Etoposide will be admixed in 0.9% sodium chloride for IV infusion and concentrations should be followed as per institution guidelines. It is recommended that concentrations should be < 0.4 mg/mL but if higher concentrations are necessary then stability will be limited to 8 hours at room temperature. For BEAM, etoposide may be prepared undiluted in PVC-free bag for administration with normal saline hydration that is given concurrently in the same lumen.

Administration

For BEAM, etoposide should be given over 1-2 hours diluted in normal saline. For CBV, etoposide may be given undiluted over 4 hours with normal saline hydration given concurrently.

Drug Interactions

Etoposide is metabolized hepatically via CYP3A4 and 3A5. Strong CYP3A4 inhibitors or inducers should be avoided during administration of etoposide.

Pharmacokinetics

Etoposide is metabolized hepatically via CYP3A4 and 3A5

Adverse Events

Myelosuppression, predominantly neutropenia and thrombocytopenia, is the most common toxicity associated with etoposide. Nausea and vomiting range from mild to severe in severity, depending on the dose. Etoposide is moderately highly emetogenic. Mucositis is also common and hypotension may be seen with rapid infusions. Alopecia is likely.

Nursing Guidelines

Monitor CBC. Neutropenia may be severe. Instruct patients to report any sign/symptoms of infection to the health care team.

Rare myocardial infarctions have been reported in patients who have received prior mediastinal XRT. Instruct patient to report any chest pain, or racing of the pulse to the health care team immediately.

Advise patient of possible mild, reversible alopecia.

A rapid infusion may cause hypotension and/or allergic reaction; administer medication over 30-60 minutes and monitor VS during administration.

Drug is a radiosensitizer and irritant. Assess IV patency before and throughout infusion. Patients who have receive prior radiation may experience radiation recall. Assess skin in these areas and monitor closely. Instruct patient to report any rash or skin changes to the health care team immediately.

Anaphylaxis is rare but has been observed. Symptoms may include hypotension, bronchospasm, fever, or chills. Have the anaphylaxis tray available.

Nausea and vomiting are usually mild. However the incidence is increased with oral administration. Premedicate with antiemetics as ordered and monitor for their effectiveness.

Instruct patient in importance of maintaining adequate hydration to avoid hyperuricemia.

Monitor liver function tests.

Etoposide solution is oil based and settles to bottom of bag or drip chamber. Be sure to agitate bag to avoid reaction to concentrated solution. Reaction would include flushing, shortness of breath, back pain, and anxiety.

Advise patient that facial flushing is common and may occur even after administration.

Monitor INR closely in patients on warfarin therapy, as etoposide may increase PT time.

May increase the toxicity of methotrexate or cyclosporine (cytotoxicity) when given concurrently.

10.6 Ara-C (Cytarabine, NSC# 63878)

Procurement

Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available as a sterile powder for reconstitution in vials of 100 mg, 500 mg, 1000 mg, and 2000 mg or a preservative free 20 mg/mL solution in 5 mL, 25 mL and 50 mL vials, or a 100 mg/mL solution in 20 mL vials. Please refer to the package insert for additional information.

Storage and Stability

Intact vials should be stored at room temperature 15-30°C (59 to 86°F). Solutions reconstituted with bacteriostatic diluents for infusion are stable for 8 days at room temperature.

Preparation

Cytarabine powder is reconstituted with sterile water for injection or 0.9% sodium chloride for injection. Solutions reconstituted with bacteriostatic should not be used for IV administration of high dose cytarabine (> 1 gm/m2), as are used in this study. Solutions for parenteral

administration should be reconstituted to a concentration of 100 mg/mL. Reconstituted solutions are further diluted in D5W or 0.9% sodium chloride for IV infusion.

Administration

Cytarabine will be administrated intravenously over 1-2 hours or per institutional guidelines.

Adverse Events

The most common adverse reactions reported with cytarabine ("usual dosage" e.g., ≤ 200 mg/m2/day) include hematologic, gastrointestinal, dermatologic, and hepatic. Myelosuppression includes neutropenia, thrombocytopenia and anemia. Cytarabine is considered highly emetogenic. In addition to nausea and vomiting, diarrhea and mucositis are reported in > 10% of patients receiving cytarabine. Alopecia is common. Rash, including hand-foot syndrome, is reported also. Mild jaundice, and elevated transaminase levels also are reported in > 10% of patients. Fever (noninfectious) is also reported among the most common adverse reactions associated with cytarabine.

Less commonly, a "cytarabine syndrome" or "Ara-C syndrome" has been reported. The syndrome may be characterized by fever, myalgia, bone pain, rash, malaise, and chest pain.

Nursing Guidelines

Can be a potent myelosuppressive agent. Monitor CBC closely. Anemia, leukopenia, and thrombocytopenia are expected. Nadir within 5-7 days with recovery expected in 2-3 weeks. Hematological toxicity is more intense if Ara-C is given as a continuous IV infusion versus an IV bolus.

Nausea and vomiting is dose-related, common, and often preventable with antiemetic drugs. Administer as ordered and assess for their effectiveness.

Instruct patient of possibility of metallic taste. The use of sugarless hard candies may lessen this effect.

Stomatitis is possible. May try dabbing Vit.E oil to lesions. Instruct patient not to swallow.

May cause pancreatitis or peritonitis. Instruct patient to report any severe or worsening abdominal pain immediately.

Monitor LFT's-elevations of LFT's may occur.

Cerebellar toxicity can occur in 16-40% of patients with more severe symptoms at higher doses. Monitor for these toxicities with each dose of Ara-C. Signs and symptoms of cerebellar toxicity can include: lethargy with progressive confusion, ataxia, nystagmus, slurred speech. Report any of these or other neurological changes to the MD immediately.

Instruct patient to report any shortness of breath or difficulty breathing as this may be a sign of a rare but life threatening pulmonary complication.

Monitor for signs of conjunctivitis and/or keratitis. This is usually prevented with prophylactic glucocorticoid eye drops.

Assess for skin rash. This may present itself as a erythema without exfoliation, or a generalized rash. Report to MD.

Monitor for "Ara-C" syndrome. This is characterized by bone and muscle pain, chest pain, fever, general weakness, reddened eyes, and skin rash. Report these to the MD, as patient may need to be treated with corticosteroids.

10.7 Melphalan (NSC# 8806)

Procurement

Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Melphalan for IV use is commercially available in 50 mg vials. The product is a lypholized powder with 20 mg povidone per vial. Also provided is 10 mL of special diluent for use in reconstituting the product. The special diluent has 0.2 g sodium citrate, 6 mL propylene glycol, 0.5 mL 95% ethanol, and sterile water. Please refer to the FDA-approved package insert for complete prescribing information.

Storage and Stability

Intact vials should be stored at room temperature (15°-30°C) and protected from light. Reconstituted solutions are chemically and physically stable for at least 90 minutes at room temperature. Solutions further diluted in 0.9% sodium chloride to a concentration of 0.1 mg/mL to 0.45 mg/mL are stable for at least 60 minutes. Solutions diluted to 1 mg/mL are reported to be physically stable for at least 4 hours at room temperature-chemical stability of this dilution is not known. Because of the relative instability of melphalan solutions, it is recommended that administration of the diluted solution be completed within 60 minutes of reconstitution. Reconstituted solutions should not be refrigerated.

Preparation

Melphalan should be prepared immediately before intended use. Each vial is reconstituted with 10 mL of the special diluent to yield a concentration of 5 mg/mL. The reconstituted solution may be diluted with 0.9% sodium chloride to a concentration of 0.1 mg/mL to 0.45 mg/mL. Alternatively, when the required concentration necessitates an unacceptable volume of fluid, the reconstituted solution may be administered undiluted or per institutional guidelines.

Administration

Melphalan should be given over 20-30 minutes and infusion must be completed within 60 minutes of preparation.

Adverse Events

The major toxicity of melphalan is bone marrow suppression, usually lasting four to eight weeks. Other toxicities include nausea, vomiting, diarrhea, and mucositis. Less common toxicities include pulmonary fibrosis, interstitial pneumonitis, vasculitis, alopecia, hemolytic anemia, and allergic reactions.

Nursing Guidelines

Hematologic toxicity is a major and dose-limiting adverse effect and is principally manifested by leukopenia and thrombocytopenia. Myelosuppression usually occurs 2-3 weeks after therapy and may persist for 6 weeks or more. Monitor CBC frequently. Instruct patient to report any signs/symptoms of infection, unusual bruising or bleeding to the health care team.

Assess for nausea and vomiting and treat symptomatically. Severe nausea and vomiting has been reported with high dose treatment. Premedicate with antiemetics before high dose IV treatment. Occasional diarrhea and stomatitis has been reported also. Treat symptomatically. Encourage good oral care.

Assess for pulmonary toxicity. Instruct patient to report any unusual cough, chest pain, or respiratory difficulties.

Anaphylaxis is possible with IV administration. Have anaphylaxis tray and necessary emergency equipment nearby when administering IV. Monitor for signs symptoms of hypersensitivity reaction, which include, rash, diaphoresis, difficulty breathing, and hypotension.

Drug is an irritant. Avoid extravasation. Establish IV patency before and throughout administration.

Monitor renal function tests. Increased nephrotoxicity of cyclosporine can be increased by melphalan.

10.8 G-CSF (filgrastim, NSC# 614629)

Procurement

Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercial filgrastim is available in 1 mL and 1.6 mL vials containing 300 mcg and 480 mcg filgrastim, and in prefilled syringes containing 300 mcg/0.5 mL or 480mcg/0.8 mL. Please refer to the FDA-approved package insert for filgrastim for product information, extensive preparation instructions, and a comprehensive list of adverse events.

Storage and Stability

Intact vials and prefilled syringes should be stored in the refrigerator at 2-8° Centigrade (36-46° Fahrenheit). Do not freeze.

Administration

Filgrastim will be administered as a subcutaneous injection. Doses should be rounded (to the vial size) per institutional guidelines.

Adverse Events

The most common side effect associated with filgrastim is medullary bone pain. Bone pain is usually reported as mild or moderate and, if necessary, may be treated with non-opioid or opioid analgesics.

Nursing Guidelines

Patients may need instruction in subcutaneous drug administration. Advise patient to take drug at the same time each day.

WBC and ANC must be monitored and communicated to medical doctor and to patient.

Patients may need to deal with financial concerns due to expense of this drug.

Keep drug refrigerated. It will be stable for ten months or more when refrigerated. There is significant loss of activity if the drug is stored above or below 2-8°C (35.6°F-46.4°F). Vials should not be shaken.

Assess for mild-moderate transient bone pain and advise patient in comfort measures.

Acetaminophen is the recommended analgesic for mild bone pain. May be beneficial to give at the time of injection.

Patients may experience rash.

Patients can experience “flu-like” symptoms– headache, fever, nausea, vomiting. Treat symptomatically and assess for effectiveness.

10.9 PEG-G-CSF (pegfilgrastim, NSC# 725961)

Procurement

Institutional pharmacy shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

6mg/0.6ml syringe.

Storage and Stability

Syringes should be kept refrigerated and stable for 48 hours at room temperature.

Administration

Injections should be given under the skin (subcutaneously).

Adverse Events

The most common side effect associated with pegfilgrastim is medullary bone pain. Bone pain is usually reported as mild or moderate and, if necessary, may be treated with non-opioid or opioid analgesics.

Nursing Guidelines

Do not administer pegfilgrastim in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

Warn patients of bone pain, arthralgia and myalgia. Treat symptomatically and monitor for effectiveness.

Instruct patients to report any peripheral edema to study team.

Headache may be seen. Treat symptomatically and monitor for effectiveness.

While rare, instruct patient to report any rash or skin changes.

10.10 Mesna (NSC# 113891)

Procurement

Mesna should be obtained from commercial supplier. Please refer to the product's commercial package insert for complete information.

Storage and Stability

Intact vials are stored at room temperature. Diluted solutions are physically and chemically stable for 24 hours under refrigeration.

Preparation

Mesna is available as an injectable solution. Mesna may be further diluted in 5% dextrose, 5% and 0.45% sodium chloride, normal saline, or lactated Ringer's solution to a final concentration of 1 to 20 mg/mL.

Administration

Mesna is often given as an intravenous injection over 5 minutes or longer. Mesna has also been given orally and as a continuous intravenous infusion.

Adverse Events

At the doses used for uroprotection, mesna is virtually non-toxic. However, the following adverse effects may be attributable to mesna:

Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain, altered taste
Dermatologic: Rash, uticaria

Other: Lethargy, headache, joint or limb pain, hypotension, fatigue

Nursing Guidelines

Doses of mesna should always be given on time. Oral mesna can be very nauseating. Provide antiemetics when oral mesna is sent home with patient. Oral mesna should be mixed with juice, water, milk, or carbonated beverage for administration. Instruct patient that all doses must be taken in their entirety and on time. If this is not possible due to nausea, patient must return to the clinic or the ER to have the missed dose and all subsequent doses administered by IV.

Instruct patient to report any rash.

Patients may experience some arthralgia/back pain. Treat symptomatically.

11.0 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the revised international working group guidelines (Lugano classification) [33].

11.1 Schedule of Evaluations:

A whole body or limited whole body PET/CT scan or a PET and CT of neck, chest, abdomen and pelvis will be performed at 3 months (+/- 1 month) for initial response assessment. This can be delayed by up to an additional month for patients undergoing post-transplant radiotherapy. Following this, either a PET/CT or a diagnostic CT of the neck, chest, abdomen, and pelvis will be repeated at 6, 12, 18, and 24 months (+/- 1 month). Additional scans are to be performed at the discretion of the treating physician at the time of suspected disease progression or off study evaluation.

Supporting documentation should be submitted, per section 6.1.1.

11.2 Measurement of Treatment/Intervention Effect

11.2.1 Target Lesions & Target Lymph Nodes

- Measured dominant lesions: Up to **six** of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.
- Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

11.2.2 Metabolic Response at 3 month (or Cycle3) Assessment

Response will be evaluated by the PET-CT based response criteria column in Section 11.2.5. Patients will also be evaluated for progressive disease (PD) by the CT-based criteria column in Section 11.2.5. Baseline refers to imaging used to document response to salvage therapy that was completed within 42 days of registration.

11.2.3 Follow-Up Assessment [at 6, 12, 18 and 24 months (+/- 1 month) and thereafter]

Response will be evaluated by the CT-based response criteria column in Section 11.2.5. Baseline refers to imaging used to document response to salvage therapy that was completed within 42 days of registration.

11.2.4 Crossover at Disease Progression

Response will be evaluated by the CT-based response criteria column in Section 11.2.5. For patients who cross over from placebo to ibrutinib, baseline refers to the tumor size at disease progression on placebo.

11.2.5 Response Assessment Table

	PET-CT Based Response	CT-Based Response
Complete Response	**Complete metabolic response (CMR)**	**Complete radiologic response (CR) (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response	**Partial metabolic response (PMR)**	**Partial remission (PR) (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value When no longer visible, 0 X 0 mm For a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase

Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not Applicable
No Response or Stable Disease	**No metabolic response (NMR)**	**Stable disease (SD)**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not Applicable
Progressive disease	**Progressive metabolic disease (PMD)**	**Progressive disease (PD) requires at least 1 of the following**
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression: An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly

Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET Deauville 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

11.3 Definitions of analysis variables

The primary clinical endpoint of this phase III trial is 24-month progression-free survival (PFS). **PFS** is defined as the time between randomization and progressive disease or death, whichever comes first. Progression is defined as PD by the CT-based response criteria. Patients alive with no history of relapse/progression are censored at the time of the last observation. **24-month PFS** is the proportion of patients who are alive and progression-free 2 years from registration.

Overall Survival is defined as the time between randomization and death from any cause. Patients alive at the time of last observation are censored at the time of the last observation.

Time to Hematopoietic Recovery. Time to ANC recovery will be the first of two consecutive days of ANC greater than or equal to 500/uL following nadir. Time to platelet engraftment will be the first day of one week without platelet transfusion when the platelet count is greater than or equal to 20,000/uL following nadir.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

12.1.1 Patients who do not progress, relapse or experience unacceptable toxicity will continue on therapy for a total of 12 cycles in the continuation phase (Cycles 2-13). After treatment is completed, patients will be followed per the study calendar in section 5.0.

12.1.2 Disease Progression or Relapse: Progression is defined as PD by the CT-based response criteria in Section 11.2.5. Remove from protocol therapy any patient with disease progression or relapse (PD) by CT-based response criteria. If a patient has progressive metabolic disease (PMD) on the Cycle 3 response assessment but does not meet criteria for PD by CT-based response criteria, they should continue treatment per protocol. Document details, including tumor measurements, on data forms.

At the time of disease progression, patients' treatment assignment will be unblinded. See section 8.3 for unblinding instructions. Patients receiving placebo will be offered therapy with ibrutinib.

After disease progression or start of alternative anticancer therapy, patients will be contacted approximately every 6 months by clinic visit or telephone, to assess survival and the use of alternative anticancer therapy until death, withdrawal of consent, loss to follow up, study closure, or 60 months have elapsed from registration, whichever occurs first.

12.1.3 Discontinuation of study agent: If the patient discontinues ibrutinib in cycle 1 or continuation cycles 2-13 for reasons other than progression or relapse and they have not withdrawn study consent, they will continue protocol follow up requirements per study calendar in section 5.0 as per active treatment. For example, imaging scans will be performed at 3, 6, 12, 18, and 24 months, and clinical follow-up at 3, 6, 9, 12, 18, and 24 months from registration, then every 6 months for up to 60 months from registration.

Once they progress or start alternative lymphoma therapy, they will be followed approximately every 6 months by clinic visit or telephone to assess survival and the use of alternative anticancer therapy until death, withdrawal of consent, loss to follow up, study closure, or 60 months have elapsed from registration.

12.2 Definitions and Follow-up Requirements

Definition of ineligible patients: A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible. Patients who are deemed ineligible may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient were to continue protocol treatment. Notification of the local IRB may be necessary per local IRB policies.

Definition of clinical follow-up: The follow-up period where the study participant is no longer receiving treatment, but is still following the study calendar for tests, exams, and correlative endpoints (e.g., specimen collection, quality of life, disease assessments as required by the study).

Definition of survival only follow-up: The follow-up period where the study participant is monitored for long-term endpoints, is no longer receiving study treatment, and is not required to follow the study calendar for tests, exams, and correlative endpoints (e.g. specimen collection, quality of life, disease assessments as required by the study). In this follow-up period, there is a schedule in which case report forms should be submitted, but the physician visits are based on the standard of care.

12.2.1 Follow-up for Ineligible Patients

Study participants who are registered to the trial but deemed ineligible must complete follow-up requirements as specified below:

Baseline, on-study, endpoint (e.g., relapse or progression), off treatment, and survival data submission required.

12.2.2 Follow-up for Patients Never Receiving Protocol Intervention

Study participants who are registered to the trial but who never go on to receive study intervention must still complete follow-up requirements as specified below:

Baseline, on-study, and off treatment-data submission required.

12.3 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:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

A total of 160 patients (80 per arm) will be randomized between ibrutinib arm and placebo arm with equal probability stratified at study entry by prior use of ibrutinib (yes vs. no), type of transplant regimen planned (CBV vs. BEAM), and time to relapse (≤ or > 12 months). This study will recruit 166 patients, including a cohort of 6 patients to investigate the safety of ibrutinib as described in section 13.7 below.

13.2 Sample Size, Accrual Time and Study Duration

Relapsed DLBCL is the second largest indication for AutoHCT after multiple myeloma. The original projections were based on a CIBMTR query of member institutions for the 4-year period of 2009 – 2012, whereby 635 DLBCL patients per year underwent an AutoHCT among the top 40 U.S. sites and 770 patients per year among the top 60 U.S. sites [Tim Fenske personal communication]. Assuming broad cooperative group and BMT-CTN participation and that 30-50% of these patients would be assigned to the ABC subtype, we expected that 231 – 385 patients would be potentially eligible every year and as many as 96 could have been enrolled. However, the screening logistics employed initially (including the subtype assignment tool) resulted in only ~13% of screened patients proceeding to registration. We made major modification at a later version that have now resulted in ~52% of patients registering. In that same period, alternative treatment strategies (CART cells, novel antibody-drug conjugates) have been approved that further limited the number of transplants being performed nationally and the number of patients enrolled on study. We expect the current accrual numbers to hold at these lower levels.

Accounting for about 5% of attrition due to dropouts or ineligibilities, this study will randomize a total of 160 patients between the two arms (80 patients per arm). From Gisselbrecht et al [7] and Vose et al [9], we expect a median PFS of the placebo arm to be about 24 months. We would consider the experimental agent clinically meaningful if its 24-month PFS is 67% or higher (odds ratio=2). Assuming that 152 (=0.95x160) patients have at least 2 year of follow-up, the asymptotic test comparing the Kaplan-Meier estimators at 2 years with 1-sided alpha=10% will have 74% of power. This design includes one interim analysis for futility after 40 randomized

patients reach the 2-year PFS end point. This study will take about 90 months (66 months for patient accrual based on a projected accrual of 2.5 patients per month and 24 months for additional follow-up).

Changes as of Update #06

As of September 17, 2018, this study has pre-registered 254 patients and has registered 32 patients (n=6 for early safety monitoring and n=26 of 296 patients required for the randomized portion of the study). The large degree of attrition is primarily due to inadequate tissue for running the LST assay, failed central review of histology, ineligibility based on LST results even among patients who are non-GCB by IHC, and patient/investigator decision to not proceed with registration due to delays in testing. These issues are being addressed by site education of tissue requirements and change in eligibility based non-GCB determination by central review (Hans algorithm). It is expected that this modification will allow for timelier randomization, decreasing attrition currently related to the extended period of time between pre-registration and registration, and decreasing tissue requirements necessary for running and interpreting the LST assay.

The 26 patients already randomized with confirmed ABC subtype by LST will be included as part of the 296 total patients required in the randomized portion of the study. Based on current available data, it is anticipated that, approximately 160 patients per year will be pre-registered going forward, with up to 96 patients (60%) lost prior to registration due to insufficient tissue (10%), failure to confirm a DLBCL diagnosis upon central path review (10%), failure to confirm non-GCB subtype upon central path review (25%), and patient/investigator decision (15%). It is therefore estimated that a total of 64 patients will be registered per year. At this rate, it is anticipated that it will take approximately 4 years to accrue the remaining 270 patients required. Accounting for 24 months of follow-up after the completion of accrual, the primary analysis is anticipated approximately 6 years after the implementation of Update #06.

Changes as of Update #09

As of November 16, 2021, this study has registered 89 patients (n=6 for early safety monitoring and n=83 patients required for the randomized portion of the study). Due to concerns over lower-than-expected accrual rate and to ensure that the study is completed in a timely manner, the total sample size for the randomized portion of the trial has been reduced from 296 patients (148 per arm) to 160 (80 per arm). Assuming a 5% attrition due to dropout or ineligibilities, we expect 152 patients (76 per arm) will be evaluable for the primary endpoint. This sample size provides 74% power at a 1-sided Type I error of 0.10 to detect an improvement in 24-month PFS probability with ibrutinib compared to placebo, assuming a 24-month PFS of 67% in the ibrutinib arm versus 50% in the placebo arm. This design includes one interim analysis for futility when 40 (26%) of randomized patients have reached the 2-year PFS endpoint. ***This interim analysis will occur in March 2022.***

13.3 Statement for Primary Endpoint

The primary clinical endpoint of this phase III trial is 24-month progression-free survival (PFS), as measured by the Kaplan-Meier estimator. PFS is defined as the time between registration and disease progression or death due to any cause, whichever comes first. Progression is defined as PD by the CT-based response criteria.

13.4 Statement for Secondary Endpoint

Secondary endpoints include overall survival (OS), progression free survival (PFS), response rate assessment following AutoHCT (at 3 months), time to hematopoietic recovery, safety and tolerability of ibrutinib therapy, incidence of secondary malignancies, and immune reconstitution.

For the patients who receive the experimental therapy after progression from the control therapy, response rate and PFS will be estimated. The baseline for PFS in these analyses will be the time of progression from the first (randomized) treatment.

13.5 Interim Analysis Design for Primary Endpoint

The primary analysis is to compare the 24-month PFS probability between the two arms using the chi-squared test for 2-sample binomial proportions. If there are any cases with PFS censored before 2 years, then we will compare the Kaplan-Meier estimates of the two arms at 2 years.

Interim Analysis: Interim analyses will be conducted when 40 randomized patients have at least 2 years of follow-up. Based on the design setting and the accrual status on November 16 2021, ***the interim analysis for futility will occur in March 2022***. At the interim analysis, the trial will be terminated for futility if the observed difference (experimental vs. control) in PFS between the two arms is < 0 (i.e., the stopping boundary is Z = 0). Otherwise, the trial will continue to the final analysis.

Final Analysis: The final analysis will be conducted when all patients have reached the 2-year follow-up. At the final analysis, if Z > 1.282 (equivalently, p-value < 0.1) it will be concluded that ibrutinib is associated with an improved 24-month PFS. Below is the operating characteristics of this design based on a simulation of 10,000 trials.

24-month PFS (%)		Prob stopping early for futility (Z < 0)	Final analysis conclusion		Power
Control	Treatment		Efficacy (Z > 1.282)	Futility	
50%	50%	43.3%	10.2%	46.6%	10.2%
	60%	22.0%	46.6%	31.5%	46.6%
	67%	10.6%	76.9%	12.5%	76.9%

Using logistic regression, multivariable analyses will be conducted to adjust for the stratification factors and other clinical predictors. If there are patients whose PFS time are censored before 2 years, then the logistic regression will be modified using the method of Jung [34] to include all patients in the analysis. We will also conduct a multivariable analysis using the Cox regression model using the raw PFS data.

13.6 Analysis Plan for Secondary Endpoints

Secondary endpoints are analyzed only at the final analysis.

Hierarchical Testing for Secondary Endpoint: If the primary comparison of 24-month PFS is significant at the overall one-sided significance level of 0.10, then the PFS hazard rates between the two arms will be compared using the log-rank test at a .10 one-sided significance level. If the log-rank test for PFS is significant at the 0.10 significance level, then we will compare the OS between the two arms using the log-rank test at a 1-sided significance level of 0.05. The marginal power for the OS comparison is provided below.

Both the primary and secondary analyses will be conducted using the intent-to-treat principle. In terms of OS, Vose *et al.* described a 2-yr OS of 66% for R-BEAM, which corresponds to an annual hazard rate of 0.207 under an exponential OS model. Thus with 160 patients (152 evaluable patients), the log-rank test with a one-sided significance level of 5% has approximately 82% of power to detect a hazard ratio (experimental vs. control) of 0.53 assuming a monthly accrual rate of 2.5 patients and all patients are followed for survival for up to 5 years. Under the design setting and the assumption of exponential distributions for PFS and patients followed for up to 5 years, we would have a power of 91% at the one-sided type I error of 10% if we used the log-rank test (instead of chi-squared test) to compare PFS between the two arms.

For each arm, the distributions of OS, PFS, and time to neutrophil and platelet engraftment will be estimated using the Kaplan-Meier method. OS, PFS, and time to neutrophil and platelet engraftment will be compared between the two arms using the log-rank test and Cox regression method adjusting for the known predictors. The metabolic response proportion following AutoHCT will be compared between the two arms using chi-squared test.

Treatment-related mortality, incidence of secondary malignancies and hematologic toxicity of ibrutinib therapy will be summarized using contingency tables.

13.7 Early Safety Monitoring

Ibrutinib has been shown to augment chemotherapy-induced cytotoxicity in ABC-like DLBCL cells [20, 35]. Ibrutinib has a low toxicity profile, and it has been safely combined in completed and currently ongoing studies with alkylator-based treatment regimens for patients with lymphoproliferative disorders. Thus, we expect its combination with preparative regimen chemotherapy to be effective and well tolerated. To ensure safety during the engraftment phase, we will hold ibrutinib following completion of the preparative regimen. Additionally, we will treat a cohort of 6 patients per open-label safety run-in (all getting ibrutinib in Cycles 1-13). These patients will not be randomized and will be excluded in the statistical analysis to compare the two arms. We require that at least 2 patients out of the 6 receive therapy with BEAMi and 2 patients with CBVi. We will consider amendment of the study if the number of patients who experience grade 3/4 unexpected toxicities is greater than or equal to 2 among the 6 patients. The expected rate of grade 3/4 unexpected toxicity for ibrutinib is about 25%. This monitoring rule has 22%, 47%, 68%, 84%, or 93% of probability to amend the study if the rate of grade 3/4 unexpected toxicity for ibrutinib arm is 15%, 25%, 35%, 45%, or 55%, respectively.

We will hold weekly teleconferences during the early safety phase to be attended by the study investigators or their representatives, the principal investigator, data management, and the statistical data center to review adverse events, accrual and other issues that arise over the course of the study. This teleconference is only required for those sites with patients on study.

13.8 Protocol-Specific Monitoring Plan

Accrual Monitoring

Accrual will be monitored closely after activation of Update #06 to ensure trial feasibility. Failure to meet accrual goals may be attributed to lower than anticipated preregistration rates and/or higher than anticipated drop-out rates between preregistration and registration. Ultimately, we will require that the observed preregistration rate is at least 75% of the targeted preregistration rate and that the drop-out rate between pre-registration and registration is no higher than 60%. Preregistration and registration rates will be reviewed in the first 6 months and in months 6-12 to ensure that at least 50% and 75%, respectively, of the projected rates are being met. In addition, the drop-out rate between pre-registration and registration and the reasons for drop-out will be reviewed with each successive group of 30 patients preregistered. If the drop-out rate is higher than 60%, the data will be discussed with the central pathology lab, Data Monitoring Committee, and the National Cancer Institute to determine whether processes can be modified to minimize drop-out and if trial completion remains feasible.

On-site Monitoring

On-site audits will be conducted according to the NCI Clinical Trials Monitoring Branch guidelines.

13.9 Inclusion of Women and Minorities

All studies must address the issue of inclusion of women and minorities in clinical research and whether gender or race/ethnicity differences in the intervention effect are to be expected.

PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	0	0	0	1
Asian	1	5	0	0	6
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	7	13	1	0	21
White	63	66	2	4	135
More Than One Race	2	0	0	0	2
Total	74	85	3	4	166

13.10 Clinical Data Update System (CDUS)

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: This study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

14.0 CORRELATIVE AND COMPANION STUDIES

All studies described in this section are integrated correlative studies in A051301 and are considered approved as part of this protocol. Analyses based on these correlative studies will be considered exploratory, and no labeling claims will be made based on them.

14.1 Imaging Correlative Science

Evaluation of the role of FDG-PET in predicting outcomes prior to (post salvage) and following AutoHCT in relapsed/refractory patients with DLBCL.

14.1.1 Background

PET/CT imaging using fluorodeoxyglucose (18F) has been shown to predict response duration, progression-free, and overall survival at the completion of first-line therapy in patients with DLBCL and other lymphomas [36]. It has consequently been incorporated in the response assessment criteria for lymphoma and has become the standard of clinical care [37]. Data from mostly retrospective or single-institution studies suggest that FDG-PET/CT assessment following salvage therapy for relapsed patients with lymphoma is also predictive of outcomes following AutoHCT [38-46]. However, there has been no prospective study in relapsed DLBCL to formally evaluate the utility of FDG-PET/CT in this setting. We propose to evaluate the hypothesis that a positive FDG-PET/CT in patients who otherwise meet criteria for chemosensitive disease during salvage therapy (study enrollment) will be

associated with inferior PFS and OS following autologous stem cell transplantation. Our secondary hypothesis is that planned therapy with ibrutinib will modify this effect. FDG-PET/CT scans obtained during salvage assessment will be acquired and centrally reviewed. We will utilize both traditional revised IWG criteria as well as the Lugano criteria to perform our analysis as well as quantitative metabolic measurements. The results of our study may validate the prognostic and predictive role of FDG-PET/CT in the relapsed DLBCL setting and allow the design of future intervention trials targeting a more selected high-risk patient population.

14.1.2 Objectives

14.1.2.1 To assess whether pre-AutoHCT positive FDG-PET is associated with inferior 24-month PFS as well as PFS and OS.

14.1.2.2 To assess whether pre-AutoHCT FDG-PET results are differentially associated with 24-month PFS, PFS, and OS in the ibrutinib versus placebo arms.

14.1.2.3 To evaluate the application of the Lugano criteria and change in quantitative measurements between pre-AutoHCT and post AutoHCT FDG-PET (e.g., delta SUV, %SUV decline and %MTV decline, and other available applicable quantitative measurements) to assess the association between changes in these variables and outcomes, such as PFS and OS.

14.1.3 Methods

PET/CT using fluorodeoxyglucose (^{18}F) (FDG) performed during salvage therapy assessment will be acquired at the time of study entry and will be centrally reviewed. Semi-quantitative and qualitative PET analysis will be performed by the Alliance imaging committee using SUV, mediastinal blood pool, and liver uptake. All patients will then receive PET/CT subsequent scans as mandated by the protocol for response assessment. We will ask that all PET/CT scans be performed at the same instrument at each institution. These PET/CT scans will be considered standard of care.

14.1.4 Statistical Design

Of those who respond to salvage therapy and go on to transplant, about 60% will be PET/CT negative by rIWG criteria. Within each arm, PFS and OS will be compared between PET/CT positive and negative groups using the two-sample log-rank test with a 2-sided alpha of 5%. Assuming that FDG-PET/CT data will be available for 90% of the patients (n=68 per arm), we will have 80% power to detect a true hazard ratio (HR) of 0.45, corresponding to a difference in median PFS of 1.25 years for PET/CT positive group vs. 2.80 years for PET/CT negative group in the placebo arm. In the treatment arm, we will have 80% power to detect a true HR of 0.40 or less, corresponding to a difference in median PFS of 2.25 years for PET/CT positive group vs. 5.68 years for PET/CT negative group in the experimental arm. Other design parameters are set at the same values as in the main trial. A Cox regression model will be conducted to regress PFS and OS on PET/CT positivity, study treatment arm, their interaction and known clinical predictors, so that the real power for PET/CT positivity effect will be higher than this power which is based on an unadjusted analysis (the 2-sample log-rank test). We will also evaluate the influence of PET/CT status on the 2-year PFS rate. Logistic regression models will be used to evaluate the influence of PET/CT status on 2-year PFS rate within treatment arms as well as across arms but where interaction effects are evaluated. With 136 evaluable patients, we will have 80% power to detect an odds ratio (OR) of 0.36 or lower. We will also conduct similar analyses using Deauville criteria with cutoffs at scores of 2 and 3, and quantitative measurements, e.g. delta

SUV, %SUV decline and %MTV decline, in place of the dichotomous FDG-PET/CT outcome. We will further estimate the positive and negative predictive values, sensitivity and specificity of PET/CT by dichotomizing the PFS and OS at 2 years (e.g. case if PFS>2 years and control otherwise). In order to investigate the prognostic value of FDG-PET positivity, we will also conduct these analyses using only the control arm.

14.2 Pharmacogenetics (Alliance A051301-PP1)

A051301-PP1 will evaluate the Pharmacogenetics of High-dose Chemotherapy and Treatment Efficacy in Relapsed/Refractory DLBCL.

14.2.1 Background

The pharmacogenomic component of this study is conducted as part of the NIH Pharmacogenomics Research Network, which is funded through a separate U01 mechanism (see http://www.nigms.nih.gov/pharmacogenomics/research_net.html) for details.

Pharmacogenetic studies will focus on the effects of candidate SNPs on pulmonary toxicity after high-dose chemotherapy followed by autologous stem cell transplant. High-dose chemotherapy administered in the setting of autologous stem cell transplantation can be associated with significant short-term (mucositis, delayed count recovery, infection) and long-term (BCNU pneumonitis, secondary malignancies) toxicities. Germline polymorphisms may affect the severity of these toxicities in individual patients, as well as treatment efficacy. We hypothesize that the null (deletion) allele of *GSTT1* is associated with pulmonary toxicity in relapsed DLBCL patients treated with high-dose chemotherapy administered in the setting of autologous stem cell transplantation.

Factors believed to contribute to chemical lung injury include oxidative stress and inflammation. Higher doses of BCNU are associated with a higher risk of pulmonary toxicity [47]. Gene expression and polymorphisms in glutathione reductase and *NQO1* (oxidative stress), TNFa, IL-1R, and others (inflammation) have been associated with lung injury [48] [49-53]. *GSTT1* encodes the glutathione transferase with the highest activity in the denitrosylation and inactivation of BCNU [54]. There is a common copy number variation of this locus, with a null allele frequency of 34-74%, based on racial ethnic background [55]. Expression of *GSTT1* is tightly correlated with gene copy number, with lowest expression in homozygous null patients (-/-)[56]. A mouse knockout for *GSTT1* is viable and has higher serum BCNU levels and higher area under the curve (AUC) after BCNU administration [57]. We hypothesize that patients with lower *GSTT1* copy number will be more susceptible to BCNU-induced pulmonary toxicity due to decreased clearance of the drug and/or more oxidative damage in lung tissue.

Other proteins are likely associated with BCNU pneumonitis as well. O(6)-methylguanine-DNA methyltransferase (MGMT) is a key enzyme involved in the excision of 06-guanine methyl or chloroethyl damage that is induced by BCNU and other agents with a similar mechanism of action. Its expression has been implicated in drug resistance and inferior clinical outcomes in patients with glioblastoma multiforme treated with these drugs [58-60]. MGMT promoter methylation status has been associated with MGMT expression and expression associated with activity and drug resistance to BCNU, temozolomide, and DTIC. The nonsynonymous SNP rs2308321 (I174V) (MAF 0.159 CEU) has been associated with expression, activity, carcinogenesis, and response to DTIC in melanoma. Additionally, the promoter SNP rs16906252 (MAF 0.120 CEU) has been associated with methylation status in tumor and normal tissue. ATP-dependent drug efflux via transmembrane transporters is a major route of elimination of cyclophosphamide and etoposide from the cytoplasm and thus, a major determinant of intracellular drug levels [61]. MDR1 glycoprotein (*ABCB1*) is the first member of this transporter family to be described in multi-drug resistant cell lines

and has since been shown to be expressed in most tissues and overexpressed in a variety of solid and hematologic malignancies. Several lines of work suggest an association between ABCB1 expression and inferior clinical outcomes in patients with DLBCL and other lymphomas in the front-line setting [62-64]. The polymorphism C3435T (rs1045642) has been previously identified to be associated with expression and function of ABCB1 [65]. Additionally, it has been implicated in toxicity and clinical efficacy of ABCB1 substrates in other studies [66-70]. In exploratory analyses, we will also evaluate the ABCB1 SNP rs1045642, and others in XRCC3, GSTP1, MDM2 snp309, and SNPs associated with etoposide cytotoxicity (rs460869, rs6588131, and rs16965867) in this patient population.

14.2.2 Objectives

14.2.2.1 To assess whether the GSTT1 null polymorphism is correlated with pulmonary toxicity after BCNU-containing conditioning regimens as part of autologous stem cell transplantation.

14.2.2.2. Secondary objectives are to assess whether other polymorphisms in the BCNU metabolism pathway or BCNU damage repair pathway(s) are associated with pulmonary toxicity after BCNU-containing conditioning regimens as part of autologous stem cell transplantation.

14.2.2.3. Additional objectives will assess whether any of the proposed polymorphisms are associated with other toxicities.

14.2.2.4 Exploratory analyses to identify polymorphisms associated with ibrutinib response will be performed.

14.2.3 Methods

Ten mL whole blood in an EDTA tube 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 Washington University (WUSTL) for DNA preparation. DNA quality will be assessed by UV spectrophotometry and by agarose gel electrophoresis. All DNA samples will be stored at WUSTL until they are distributed to the appropriate laboratory for genotyping. For the *GSTT1* null allele, samples will be genotyped using previously established assays (Taqman, based) [55]. Assays for other polymorphisms will be done according to previously established assays as well. Phenotypic data will be extracted from the Alliance database by the Alliance Statistical Center. Statistical analyses will be conducted under the direction of the responsible Alliance faculty statistician.

14.2.4 Statistical Design

The primary statistical objective for this companion study is to investigate the association between the *GSTT1* null allele and BCNU-induced lung toxicity. The response phenotype will be quantified using standard CTCAE criteria, and changes in DLCO from baseline. Specifically, we hypothesize that patients with null alleles of *GSTT1* (-/- or +/-) will have a higher risk of pulmonary toxicity after the BCNU-containing conditioning regimens used in this protocol. The analysis will be stratified by BCNU dosage, with patients categorized as receiving either the “low” (300 mg/m2) or “high” (15 mg/kg) dose, in order to control for the different preparatory regimens.

The number of eligible patients to be registered to this study and randomized is 160. Assuming 5% attrition due to ineligibility and dropout gives a sample size of 152 eligible patients (76 per arm). We will perform an analysis with adjustment for ancestry, but given the limited power to examine this association in minority subjects, the primary analysis

population will be the subset of patients who are of Northern European ancestry. Genome-wide association studies conducted by the investigators suggest that using self-reported race and ethnicity is a reliable surrogate marker for determining Northern European ancestry in absence of genome-wide data. 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 provide usable samples to pharmacogenomic studies. The power calculations shown below will be based on the assumption that 110 patients will be available for these analyses. It is noted that this is the smallest expected sample size. All patients who provide consent and usable samples will be included in the proposed pharmacogenomic studies.

The reported relative allelic frequency for the null allele ("-") is q=0.34.[55] The corresponding genotypic frequencies are inferred assuming Hardy-Weinberg, and for the two groups are 0.**44** (+/+) and 0.56 (+/- or -/-), based on allele frequency in Caucasian-Americans. We also assume that the toxicity rates are 0.15 in the patients who receive BEAM conditioning and 0.30 in the patients who receive CBV conditioning [71-73]. We estimate that approximately 2/3 of the patients will receive BEAM and 1/3 will receive CBV. With a weighted average, we assume then that overall pulmonary toxicity rates will be 0.2.

We assume that the event probability in this population is 0.2 and that it is expressible as a mixture of the form 0.2=(0.66^2)*p0+(1-0.66^2)*p0*GRR, where p0 is the probability of toxicity if the genotype is +/+ and GRR denotes the genotype relative risk. The power at the two-sided 0.05 level is 0.8 when GRR=2.41.

As secondary objectives, we will assay candidate variants and loci hypothesized to be associated with clinical phenotypes (e.g., progression-free survival, overall survival or other toxicities) or other eQTLs.

All SNPs will be evaluated for deviation from Hardy-Weinberg. In the absence of a hypothesized effect, the association analyses will be powered for allele dosing (i.e., additive) effects. To this end, the Cochran-Armitage test (for binary endpoints), Jonkheere-Terpstra test (for quantitative traits including biomarker or gene expressions in serum or tumor RNA) and the Cox score test (for censored time-to-event outcomes) will be used to quantify marginal associations. Multivariable models, with molecular, clinical and demographic variables, will be constructed using conditional inference trees and random forests.

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. This proposed study and any other correlative studies to be performed on collected specimens will be submitted to NCI as separate research protocols for consideration and approval.

[redacted]

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Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

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APPENDIX I 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 entered into Medidata Rave at the time of registration.

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 it can be										As good as it can be

APPENDIX II CYP3A INDUCERS AND INHIBITORS

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A enzymes. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist. Please review the current literature for other agents which may have interactions with ibrutinib. For the most comprehensive effect of CYP3A inhibitors or inducers on ibrutinib/placebo exposure, please refer to the current version of the IB.

Ibrutinib/placebo is metabolized primarily by CYP3A4. Concomitant use of ibrutinib/placebo with drugs that strongly or moderately inhibit CYP3A can increase ibrutinib/placebo exposure. Dose adjustment of ibrutinib/placebo due to concomitant use of CYP3A inhibitors should follow the table below.

Dose Modification Guidance for CYP3A Inhibitors/Inducers

Patient Population	**Co-administered Drug**	**Recommended Ibrutinib/Placebo Dose for the Duration of the Inhibitor Use[a]**
B-Cell Malignancies	Mild CYP3A inhibitors	420 mg or 560 mg once daily per indication. No dose adjustment required.
	Moderate CYP3A inhibitors	280 mg once daily.
	Voriconazole Posaconazole at doses less than or equal to suspension 200 mg BID	140 mg once daily.
	Other strong CYP3A inhibitors Posaconazole at higher doses[b]	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib. If the benefit outweighs the risk, and long-term dosing with a CYP3A inhibitor is required (more than seven days), reduce ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.
Chronic Graft versus Host Disease	Mild CYP3A inhibitors	420 mg once daily. No dose adjustment required.
	Moderate CYP3A inhibitors	420 mg once daily. No dose adjustment required.
	Voriconazole Posaconazole at doses less than or equal to suspension 200 mg BID	280 mg once daily.

	Posaconazole at higher doses[b]	140 mg once daily.
	Other strong CYP3A inhibitors	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib/placebo. If the benefit outweighs the risk and long-term dosing is required (more than seven days), reduce ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.

[a] Monitor for adverse reactions to ibrutinib and interrupt or modify dose as recommended (see Section 8.2).

[b] Posaconazole at higher doses (posaconazole suspension 200 mg three times daily or 400 mg twice daily, posaconazole IV injection 300 mg once daily, posaconazole delayed-release tablets 300 mg once daily).

After discontinuation of a CYP3A inhibitor, resume previous dose of ibrutinib/placebo.

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

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

Short courses (≤ 14 days) of steroid treatment for non-cancer related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use, engraftment syndrome and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted. For suspected BCNU pneumonitis requiring longer term steroid therapy, ibrutinib/placebo should be held until patients are clinically stable and resumed with caution without a dose modification.

APPENDIX III ALLIANCE A051301 MEDICATION CALENDARS

PATIENT MEDICATION DIARY (Cycle 1) – Ibrutinib/Placebo

Today's date: _____ **Cycle #: 1**

Total Daily Dose: _____

Number of capsules given: _____

Patient Name: _____ (*initials acceptable)* **Patient Study ID:** _____

(To be completed by RN)

INSTRUCTIONS TO THE PATIENT:

1. You will take your dose of **ibrutinib/placebo once a day on days -6 to -1.**
2. Record the date, the number of capsules you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
3. 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
4. Ibrutinib/placebo should be taken at the same time each day. If you miss a dose of ibrutinib/placebo, you should take it as soon as possible, as long as it is on the same day. You should not take two doses of ibrutinib/placebo on the same day to make up for missed doses.
5. Please return this form to your physician when you go for your next appointment.

DAY	DATE	TIME		# of capsules taken	Comments
Example	*03/09/2015*	*9:00*	*AM*	*4 capsules*	
-6					
-5					
-4					
-3					
-2					
-1					

Physician's Office will complete this section:

Date patient started protocol treatment: _____

Date patient was removed from study: _____

Total number of capsules administered to the patient this cycle: _____

Total number of capsules returned by the patient this cycle: _____

Patient signature: _____ **Date:** _____

Physician/RN signature: _____ **Date:** _____

PATIENT MEDICATION DIARY (Cycles 2-13) – Ibrutinib/Placebo

Today's date: _____ **Cycle #:** _____

Total Daily Dose: _____

Number of capsules given: _____

Patient Name: _____ (*initials acceptable)* **Patient Study ID:** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **ibrutinib/placebo**.
2. You will take your dose of **ibrutinib/placebo once a day on days 1-28.**
3. Record the date, the number of capsules 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. Ibrutinib/placebo should be taken at the same time each day. If you miss a dose of ibrutinib/placebo, you should take it as soon as possible, as long as it is on the same day. You should not take two doses of ibrutinib/placebo on the same day to make up for missed doses.
6. Please return this form to your physician when you go for your next appointment.

DAY	DATE	TIME		# of capsules taken	Comments
Example	*03/09/2015*	*9:00*	*AM*	*4 capsules*	
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					

22					
23					
24					
25					
26					
27					
28					

Physician's Office will complete this section:

Date patient started protocol treatment: _____

Date patient was removed from study: _____

Total number of capsules administered to the patient this cycle: _____

Total number of capsules returned by the patient this cycle: _____

Patient signature: _____ Date: _____

Physician/RN signature: _____ Date: _____

APPENDIX IV COLLABORATIVE AGREEMENT PROVISIONS

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing 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 CHILD-PUGH SCORE

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

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

Source:

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