Protocol Clarification Letter

October 18, 2019

Protocol 201809111

"*A pilot study of acalabrutinib with alternating cycles of bendamustine / rituximab and cytarabine / rituximab for untreated mantle cell lymphoma*"

The purpose of this letter is clarify the intent of the protocol.

10.0 Study Calendar

The protocol currently reads:

Tests and observations	Baseline examination[1]	Treatment phase[2]	EOT[17]	Follow-up[3]
Informed consent	X			
Physical exam	X	X		
Medical history	X			
Medication Review[18]	X	**X**		
Performance status	X			
Toxicity assessment[4]	X	X	X[15]	
Pill diary		X		
Review of medical record for progression and survival				X
Laboratory Studies				
CBC with differential[5]	X	X		
CMP[6]	X	X		
Uric acid	X	X		
LDH	X	X		
Serum pregnancy test [7]	X			
HIV-1/2 antibody	X			
Hepatitis B surface antigen, surface antibody, and core antibody[8]	X			
Hepatitis C antibody[9]	X			
MIPI score[10]	X			
PET[11]	X	X	X	
Bone marrow aspiration and biopsy[12]	X	X	X	
EKG	X			
Correlative Studies				
Ki-67 (WU pathology review)[13]	X			

Blood for immune biomarkers[14]	X	X	X	
Lymphoma tissue for genomic alterations and MRD assessment	X			
Oral rinse	X			
Blood for MRD assessment[14]	X	X	X	
Bone marrow aspiration for research[16]	X	X[12]		

Notes:

1. All baseline examinations are to be performed within 28 days of the start of therapy

2. Treatment phase begins with first dose of acalabrutinib (Day 1). Tests, observations, and laboratory studies will be performed on Day 1 of each cycle.

3. The frequency of follow-up after completion of protocol treatment is per investigator's discretion. Review of the medical record will occur on an every 6-month basis for 5 years from study entry to collect data on relapse and survival.

4. Only toxicities which worsen from baseline need be collected, and only the worst grade per cycle need be recorded. Toxicity will be assessed from time of treatment initiation until the end-of-study restaging visit, approximately one month after the last dose of chemotherapy.

5. CBC with differential will be performed on Day 1 each cycle. On cycles 1, 3, and 5 the CBC will be repeated between day 10 and day 14. On cycles 2, 4, and 6 the CBC will be repeated at least twice between days 8-14 and twice between days 15-21.

6. CMP will be performed during screening and on Day 1 of each cycle

7. For women of child bearing potential. Perform within 14 days of study entry.

8. Subjects who are hepatitis B core antibody positive but surface antigen negative will need negative polymerase chain reaction (PCR) prior to enrollment. Hepatitis B surface antigen positive or PCR positive patients are ineligible.

9. Subjects who are hepatitis C antibody positive will need negative PCR prior to enrollment. Patients with PCR positive hepatitis C are ineligible.

10. The mantle cell IPI (MIPI) calculator can be accessed at http://www.european-mcl.net/en/clinical_mipi.php

11. PET scans are required for every restaging scan while on protocol. PET scans will be performed at baseline, after Cycle 3, and after Cycle 6. Patients who come off treatment early for reasons other than progression who are suspected to be responders should have an EOT assessment with PET imaging.

12. Bone marrow aspirate will be collected at baseline if the patient has not already had a bone marrow biopsy performed prior to enrolling to the study. If marrow is involved at baseline, repeat bone marrow aspiration and biopsy is required after 6 cycles of chemotherapy. Patients who come off treatment early for reasons other than progression who are suspected to be responders should have an EOT bone marrow aspiration and biopsy if they had a baseline assessment.

13. Pathology review of the patient's baseline diagnostic tissue, including lymph node, bone marrow biopsy, or blood, will include an immunohistochemical assessment of Ki-67. If the Ki-67 is already available in the WU pathology report at time of screening, the test does not need to be repeated. The result is not required at the time of patient enrollment.

14. Peripheral blood will be collected at baseline, end of Cycle 3, 4-6 weeks after Cycle 6 Day 1, and at discontinuation of treatment (if prior to Cycle 6). See Section 9.0.

15. Adverse events will be tracked for 30 days after the last dose of study treatment. Refer to Section 7.6 for details. If the investigator becomes aware of any SAEs or deaths that are causally attributed to acalabrutinib after the 30-day time period, they must be reported to AstraZeneca.

16. Only if required clinically.

17. End of treatment visit will take place 4-6 weeks after Cycle 6 Day 1.

18. Medication review at baseline and at Day 1 of each cycle to verify that patients is not taking PPIs or CYP3A4 inhibitor/inducers.

We wanted to clarify how the protocol criteria is implemented:

Tests and observations	Baseline examination[1]	Treatment phase[2]		EOT[18]	Follow-up[3]
Informed consent	X				
Physical exam	X	X			
Medical history	X				
Medication Review[19]	X	**X**			
Performance status	X				
Toxicity assessment[4]	X	X		X[16]	
Pill diary		X			
Review of medical record for progression and survival					X
Laboratory Studies					
CBC with differential[5]	X	X			
CMP[6]	X	X			
Uric acid	X	X			
LDH	X	X			
Serum pregnancy test [7]	X				
HIV-1/2 antibody	X				
Hepatitis B surface antigen, surface antibody, and core antibody[8]	X				
Hepatitis C antibody[9]	X				
MIPI score[10]	X				
PET[11]	X	X		X	
Bone marrow aspiration and biopsy[12]	X	X		X	
EKG	X				
Treatment Administration		C 1 – 3	C 4 - 6		
Acalabrutinib		X	X		
Rituximab		X	X		
Bendamustine		X			
Cytarabine			X		
Growth Factor[13]			X		
Correlative Studies					
Ki-67 (WU pathology review)[14]	X				
Blood for immune biomarkers[15]	X	X		X	
Lymphoma tissue for genomic alterations and MRD assessment	X				
Oral rinse	X				
Blood for MRD assessment[14]	X	X		X	
Bone marrow aspiration for research[17]	X	X[12]			

Notes:

1. All baseline examinations are to be performed within 28 days of the start of therapy
2. Treatment phase begins with first dose of acalabrutinib (Day 1). Tests, observations, and laboratory studies will be performed on Day 1 of each cycle.
3. The frequency of follow-up after completion of protocol treatment is per investigator's discretion. Review of the medical record will occur on an every 6-month basis for 5 years from study entry to collect data on relapse and survival.
4. Only toxicities which worsen from baseline need be collected, and only the worst grade per cycle need be recorded. Toxicity will be assessed from time of treatment initiation until the end-of-study restaging visit, approximately one month after the last dose of chemotherapy.
5. CBC with differential will be performed on Day 1 each cycle. On cycles 1 - 3 the CBC will be repeated between day 10 and day 14. On cycles 4 - 6 the CBC will be repeated at least twice between days 8-14 and twice between days 15-21.
6. CMP will be performed during screening and on Day 1 of each cycle
7. For women of child bearing potential. Perform within 14 days of study entry.
8. Subjects who are hepatitis B core antibody positive but surface antigen negative will need negative polymerase chain reaction (PCR) prior to enrollment. Hepatitis B surface antigen positive or PCR positive patients are ineligible.
9. Subjects who are hepatitis C antibody positive will need negative PCR prior to enrollment. Patients with PCR positive hepatitis C are ineligible.
10. The mantle cell IPI (MIPI) calculator can be accessed at http://www.european-mcl.net/en/clinical_mipi.php
11. PET scans are required for every restaging scan while on protocol. PET scans will be performed at baseline, after Cycle 3, and after Cycle 6. Patients who come off treatment early for reasons other than progression who are suspected to be responders should have an EOT assessment with PET imaging.
12. Bone marrow aspirate will be collected at baseline if the patient has not already had a bone marrow biopsy performed prior to enrolling to the study. If marrow is involved at baseline, repeat bone marrow aspiration and biopsy is required after 6 cycles of chemotherapy. Patients who come off treatment early for reasons other than progression who are suspected to be responders should have an EOT bone marrow aspiration and biopsy if they had a baseline assessment.
13 Growth factors may be initiated during cycles 1-3 at the discretion of the treating physician per institutional guidelines. Mandatory growth factors will be administered as per institutional guidelines within 72 hours of completion of cycles 4-6 of chemotherapy. On-body injector may be used at the discretion of the treating physician.
14. Pathology review of the patient's baseline diagnostic tissue, including lymph node, bone marrow biopsy, or blood, will include an immunohistochemical assessment of Ki-67. If the Ki-67 is already available in the WU pathology report at time of screening, the test does not need to be repeated. The result is not required at the time of patient enrollment.
15. Peripheral blood will be collected at baseline, end of Cycle 3, 4-6 weeks after Cycle 6 Day 1, and at discontinuation of treatment (if prior to Cycle 6). See Section 9.0.
16. Adverse events will be tracked for 30 days after the last dose of study treatment. Refer to Section 7.6 for details. If the investigator becomes aware of any SAEs or deaths that are causally attributed to acalabrutinib after the 30-day time period, they must be reported to AstraZeneca.
17. Only if required clinically.
18. End of treatment visit will take place 4-6 weeks after Cycle 6 Day 1.
19. Medication review at baseline and at Day 1 of each cycle to verify that patients is not taking PPIs or CYP3A4 inhibitor/inducers.

This language clarification will be updated in the next protocol amendment.

If you have any questions, please contact me or the regulatory coordinator (Danielle Rancilio, dmrancilio@wustl.edu, 314-286-1198).

Regards,

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A pilot study of acalabrutinib with bendamustine / rituximab followed by cytarabine / rituximab for untreated mantle cell lymphoma

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Protocol #: 201809111
Version Date: 07/31/19

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Study Drug(s): Acalabrutinib
Bendamustine
Cytarabine
Rituximab

IND #: 140805
ClinicalTrials.gov #: NCT03623373

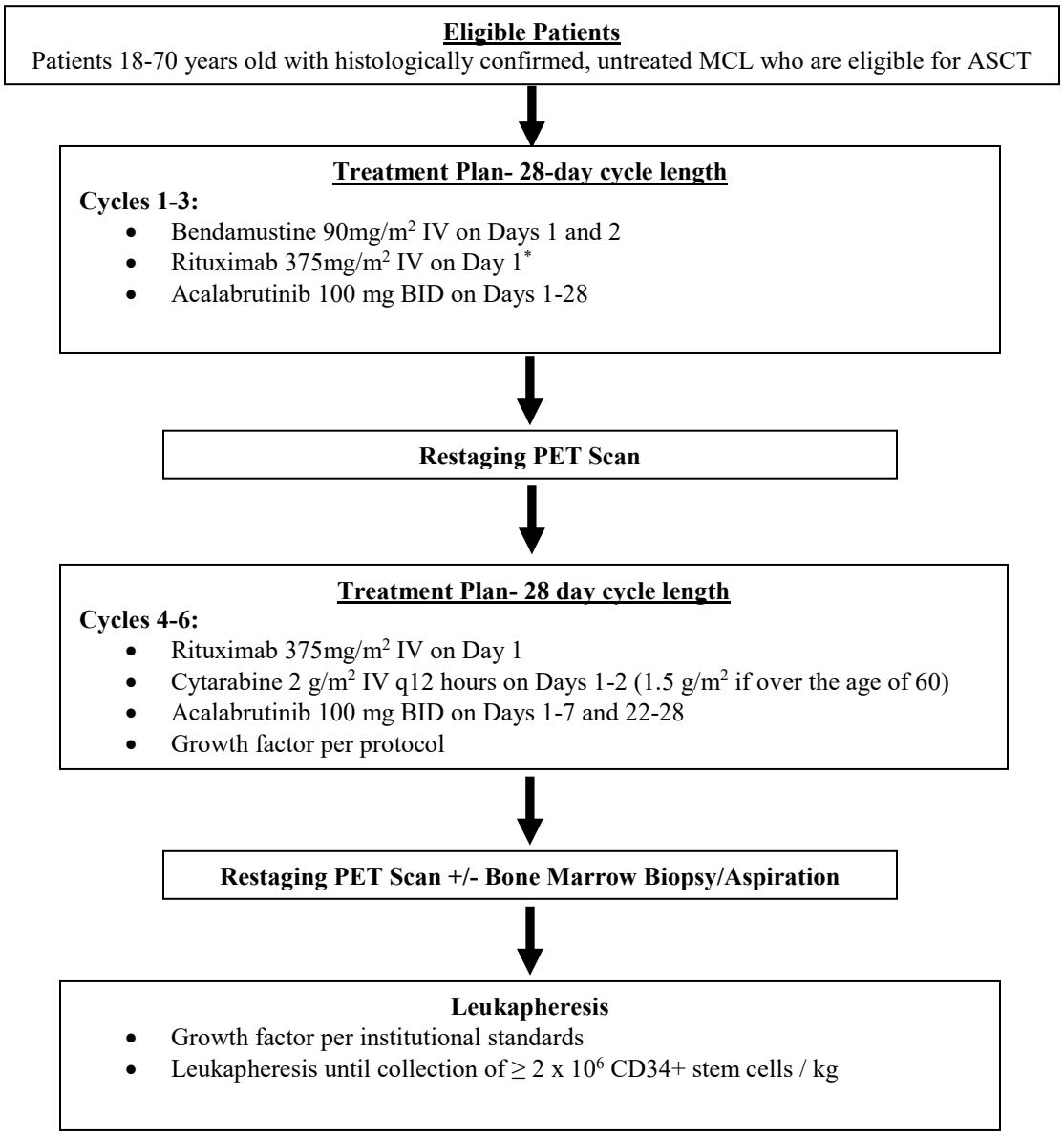
A pilot study of acalabrutinib with bendamustine / rituximab followed by cytarabine / rituximab for untreated mantle cell lymphoma

Protocol Revision History

Initial Approval Version	**09/17/2018**
Amendment #1 Version	**11/05/2018**
Amendment #2 Version	07/31/2019

A pilot study of acalabrutinib with bendamustine / rituximab followed by cytarabine / rituximab for untreated mantle cell lymphoma

SCHEMA



*Rituximab may be administered on Cycle 1 Day 1 or Day 2 at investigator's discretion in order to limit the risk of first infusion reactions

Table of Contents

1.0 BACKGROUND AND RATIONALE

1.1 Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is an incurable aggressive subtype of non-Hodgkin lymphoma (NHL) comprising approximately 7% of all adult NHL. Translocation t(11;14) and overexpression of cyclin D1 are the defining genetic characteristics in MCL, facilitating malignant transformation by dysregulation of the cell cycle (Rimokh 1994). Cyclin D1 is not expressed in normal B lymphocytes.

The incidence of MCL is approximately 4-8 cases per million persons per year, and increases with age. The median age at diagnosis is 65 years and patients typically present with advanced stage disease with associated bone marrow and blood involvement (Argatoff 1997, Bosch 1998). While combination chemotherapy and stem-cell transplant provide high response rates in the frontline setting, most of these patients eventually relapse and die from their disease (Romaguera 2010). Median OS from initial diagnosis varies from 18 to 61 months depending on prognostic risk category at baseline (Hoster 2008). Median PFS for relapsed MCL varies from 4 to 14 months (Wang 2013, Goy 2013). Thus, more effective frontline regimens for MCL are needed.

1.2 Frontline Therapeutic Options for MCL

To date there is no standard induction regimen for MCL and it remains an incurable disease with conventional therapy. The use of autologous stem cell transplantation in first remission is associated with an improvement in progression-free survival and thus conventional chemoimmunotherapy (e.g rituximab / cyclophosphamide / doxorubicin / vincristine / prednisone [R-CHOP], rituximab / cyclophosphamide / vincristine / prednisone [R-CVP], benadmustine / rituximab [BR]) followed by autologous transplant is generally the preferred therapeutic approach.

Several trials have shown an important role for cytarabine-based regimens prior to autologous transplant. To date the treatments associated with the longest PFS are the cytarabine and ASCT containing regimens from the Nordic MCL2 (Geisler 2012, Eskelund 2016) and the European Mantle Cell Lymphoma Network (Hermine et al, 2016), with median PFS of 8.5 years. Both of these regimens use R-CHOP as a component of therapy. However, it now has been shown in two randomized Phase 3 studies (the StIL trial and the BRIGHT trial) that bendamustine-rituximab (BR) was superior to R-CHOP in terms of CR rates and longer PFS with no increase in toxicity (Rummel 2013, Flinn 2014). In fact, a recently published phase II study of BR for 3 cycles followed by rituximab/high dose cytarabine for 3 cycles has shown impressive CR and MRD negativity (90%) rates in a small cohort of transplant-eligible patients (Armand 2016).

1.3 Bruton Tyrosine Kinase Inhibition in MCL

Bruton tyrosine kinase (Btk) is a non-receptor enzyme in the Tec kinase family that is expressed among cells of hematopoietic origin, including B-cells, myeloid cells, mast cells,

and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration (Khan 2001, Mohamed 2009, Bradshaw 2010). In addition, Btk-dependent activation of mast cells, myeloid cells, and other immunocytes in peritumoral inflammatory stroma has been shown to sustain the complex microenvironment needed for lymphoid and solid tumor maintenance (Soucek 2011, Ponader 2012, de Rooij 2012). Taken together, these findings suggest inhibition of Btk may offer an attractive strategy for treating B-cell neoplasms, other hematologic malignancies, and solid tumors.

Several studies have shown that targeting the B-cell receptor (BCR) signaling pathway by inhibiting Bruton tyrosine kinase (BTK) produces significant clinical benefit in patients with NHL, including MCL. Ibrutinib, has demonstrated substantial efficacy in patients with relapsed MCL based on data from a single-arm Phase 2 study of 111 patients (Wang 2013). Recent data from a Phase 1/1b study of ibrutinib plus BR, which included 17 patients with previously untreated or relapsed or refractory (R/R MCL), recently reported a CR rate of 76% (Maddocks 2015). A randomized Phase 3 study of frontline ibrutinib plus BR in patients with MCL is currently ongoing (clinicaltrials.gov; NCT01776840).

1.4 Rationale for Combining Acalabrutinib with Cycles of Bendamustine and Rituximab followed by acalabrutinib with cycles of cytarabine and rituximab

As previously mentioned, a recently published phase II study of BR for 3 cycles followed by rituximab/high dose cytarabine for 3 cycles has shown impressive CR and MRD negativity (90%) rates in a small cohort of transplant-eligible patients (Armand 2016).
To maintain excellent results and improve tolerability, Washington University (Kahl – PI) has piloted a regimen of BR with alternating cycles of high dose cytarabine –rituximab (CR). Results were as expected, with all patients successfully completing stem cell collections (NCT02728531). We have pooled our results with the Dana-Farber Cancer Institute (DFCI) trial and this combined experience has been submitted for publication. The pooled experience suggests similar tolerability between the DFCI approach and the Wash U approach. However, the DFCI approach is simpler with regards to management of toxicities and dose modificaitons. Therefore, we plan to adopt the DFCI version of the regimen for combination with novel agents. The most promising novel agent in MCL is acalabrutinib.

Acalabrutinib was specifically designed to be a more potent and selective inhibitor of BTK, and unlike ibrutinib, does not inhibit ITK and TXK, 2 members of the Tec kinase family (Covey 2015). Preclinical data indicates that this lack of inhibition against ITK and TXK may preserve natural killer (NK) cell function, and therefore may offer the potential for better synergy with rituximab (Rajasekaran 2014).

Recently a phase 2 study of acalabrutinib as monotherapy in relapsed/refractory MCL (ACE-LY-004 study) has shown high ORR (81%) as well as CR (40%) with durable and clinically meaningful responses (at 15.2 months median PFS and OS not yet reached). This combined with a favorable safety profile, with a low frequency and severity of adverse events and few discontinuations due to AE. (Wang 2017). Other trials involving

acalabrutinib in combination with BR (NCT02717624) and with rituximab (NCT02180711) are ongoing providing safety data for the combination of acalabrutinib with these regimens.

Our pilot study is designed to evaluate the efficacy and safety of acalabrutinib plus BR followed by acalabrutinib plus CR in subjects with treatment naïve MCL, as a preparation for a larger cooperative group trial with the goal of achieving a standard induction regimen for MCL in transplant eligible patients. We hypothesize that the addition of acalabrutinib to BR/CR regimen will prove safe and increase the CR rate as well as MRD negativity pre-transplant, thus improving clinical outcomes.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the stem cell mobilization success rate in subjects with MCL treated with acalabrutinib combined with the regimen of bendamustine and rituximab and cytarabine and rituximab. Stem cell mobilization success is defined as a yield of $>2x10^6$ CD34+ stem cells/kg with a maximum of 5 courses of apheresis.

2.2 Secondary Objectives

1. To determine the safety and tolerability of acalabrutinib plus BR/CR in subjects with MCL.
2. To estimate the overall response rate (ORR = CR + PR) of subjects with MCL treated with acalabrutinib plus BR/CR.
3. To estimate the pre-transplant complete response rate of subjects with MCL treated with acalabrutinib plus BR/CR.
4. To estimate the progression-free survival (PFS) of subjects with MCL treated with acalabrutinib plus BR/CR.
5. To estimate the overall survival (OS) of subjects with MCL treated with acalabrutinib plus BR/CR.

2.3 Exploratory Objective

To assess MRD negativity throughout and after completion of induction therapy.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically confirmed mantle cell lymphoma with documented expression of Cyclin D1 by immune-histochemical stains and/or t(11;14) by cytogenetics or FISH.

2. Presence of evaluable disease by PET imaging per the Lugano classification.

3. Eligible for autologous stem cell transplantation.

4. Between 18 and 70 years of age, inclusive.

5. ECOG performance status ≤ 2 (see Appendix A)

6. Normal bone marrow and organ function as defined below:
   a. Absolute neutrophil count ≥ 1,000/mcL unless, in the opinion of the treating physician, neutropenia is due to splenomegaly or bone marrow involvement
   b. Platelets ≥ 100,000/mcL unless, in the opinion of the treating physician, thrombocytopenia is due to splenomegaly or bone marrow involvement
   c. Total bilirubin ≤ 2.0 x IULN and AST(SGOT)/ALT(SGPT) ≤ 3.0 x IULN except when, in the opinion of the treating physician, elevation is due to direct involvement of lymphoma (e.g. hepatic infiltration or biliary obstruction due to lymphoma) or Gilbert's disease
   d. Creatinine ≤ IULN OR creatinine clearance ≥ 40 mL/min for patients with creatinine levels above institutional normal

7. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

8. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Any previous chemotherapy or radiation for mantle cell lymphoma. Short course of steroids for symptom relief prior to presentation is permissible.

2. Symptomatic meningeal or parenchymal brain lymphoma.

3. Prior exposure to a BTK inhibitor.

4. Currently receiving any other investigational agents.

5. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to acalabrutinib, rituximab, cytarabine, bendamustine, or other agents used in the study.

6. Received a live virus vaccination within 28 days of first dose of study drug.

7. Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment), or intravenous anti-infective treatment within 2 weeks before first dose of study drug.

8. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) > 480 msec at screening. Exception: subjects with controlled, asymptomatic atrial fibrillation during screening are allowed to enroll on study.

9. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.

10. Active bleeding or history of bleeding diathesis (eg, hemophilia or von Willebrand disease).

11. Uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura).

12. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.

13. Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer.

14. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug.

15. Prothrombin time (PT)/INR or aPTT (in the absence of lupus anticoagulant) >2x ULN. Exception: Subjects receiving warfarin are excluded; however, those receiving other anticoagulant therapy who have a higher INR/aPTT may be permitted to enroll to this study after discussion with the PI.

16. Requires treatment with proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.

17. History of significant cerebrovascular disease/event, including stroke or intracranial hemorrhage, within 6 months before the first dose of study drug.

18. Major surgical procedure within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or

complications from the intervention before the first dose of study drug.

19. Subjects with serologic status reflecting active viral hepatitis B or C infection. Subjects who are hepatitis B core antibody positive but surface antigen negative will need negative polymerase chain reaction (PCR) prior to enrollment. Hepatitis B surface antigen positive or PCR positive patients will be excluded. Subjects who are hepatitis C antibody positive will need negative PCR prior to enrollment. Subjects with positive hepatitis C PCR will be excluded.

20. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative serum pregnancy test within 14 days of study entry.

21. Known HIV-positivity on combination antiretroviral therapy because of the potential for pharmacokinetic interactions with acalabrutinib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

Consenting and eligible patients (people aged 18 to 70 with histologically confirmed, untreated MCL who are eligible for ASCT) will receive six 28-day cycles of treatment. Cycles 1-3 will consist of bendamustine 90 mg/m^2 on Days 1 and 2, rituximab 375 mg/m^2 on Day 1, and acalabrutinib 100 mg BID on Days 1 through 28. Cycles 4-6 will consist of rituximab 375 mg/m^2 on Day 1, cytarabine 2 g/m^2 (1.5 g/m^2 if over the age of 60) q12 hours on Days 1 and 2, acalabrutinib 100 mg BID on Days 1 through 7 and 22 through 28 (one week on, two weeks off, one week on), and growth factors as per institutional standard. After Cycles 3 and 6, patients will be restaged. After Cycle 6, patients will undergo leukapheresis for the collection of at least 2 x 10^6 CD34+ stem cells/kg. The purpose of this study is to determine the stem cell mobilization success rate in these patients.

5.1 WU Pathology Review of Ki-67

As per institutional practice, WU pathologists will review all in-house and outside diagnostic specimens available for each patient prior to treatment. In addition to histological confirmation of mantle cell lymphoma, Ki-67 will be assessed by immunohistochemistry at baseline. The Ki-67 proliferative index is a biologic marker with prognostic significance in advanced-stage MCL. If Ki-67 staining was performed at an outside facility, it will not need to be repeated at Washington University.

5.2 Premedication Administration

For acalabrutinib: No specific premedications or supporting medications are required in conjunction with acalabrutinib administration.

For rituximab: Pre-medicate before each infusion with acetaminophen and an antihistamine in accordance with prescribing information or institutional standards.

For bendamustine: Institutional standards for antiemetic prophylaxis should be followed. Consider antipyretic and antihistamine prophylaxis for subjects with a previous Grade 1 or 2 infusion reaction to bendamustine.

For cytarabine: No specific premedications are required in conjunction with cytarabine. See below discussion for supportive care discussion.

5.3 Agent Administration

5.3.1 Acalabrutinib

Acalabrutinib is an oral drug taken twice per day at a dose of 100 mg approximately every 12 hours on every day of each 28-day cycle during Cycles 1-3 and on Days 1 through 7 and 22 through 28 during Cycles 4-6. The capsules should be swallowed intact with water and with or without food. Subjects should not attempt to open capsules or dissolve them in water. Compliance will be assessed through use of a medication diary (Appendices B and C).

If a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the next dose. If it has been > 3 hours, the dose should not be taken and the subject should take the next dose at the scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Guidance on co-administration of acalabrutinib with agents that affect gastric pH is provided below.

On days when other drugs are administered, they may be given before or after the first acalabrutinib dose of the day.

5.3.2 Bendamustine

Bendamustine will be administered at a dose of 90 mg/m^2 IV over 30 minutes on Days 1 and 2 of Cycles 1-3. (Rate of administration may vary according to institutional standards.)

5.3.3 Rituximab

In Cycle 1, rituximab will be administered at a dose of 375 mg/m^2 IV on Day 1 or 2 at the investigator's discretion in order to reduce the risk of a first infusion reaction. Rituximab will be given on Day 1 of Cycles 2 through 6. The rituximab infusion may be completed on Day 2 if logistical considerations result in a delay.

5.3.4 Cytarabine

On Days 1 and 2 of Cycles 4-6, for patients up to age 59 cytarabine will be administered at a dose of 2 g/m^2 IV every 12 hours for a total of 4 doses. Patients between ages 60-70 will receive 1.5 g/m^2 IV every 12 hours for a total of 4 doses.

5.3.5 Growth Factors

Mandatory growth factors will be administered as per institutional guidelines within 72 hours of completion of cycles 4-6 of chemotherapy. On-body injector may be used at the discretion of the treating physician.

Growth factors may be initiated during cycles 1-3 at the discretion of the treating physician per institutional guidelines.

5.4 Definitions of Evaluability

Patients who do not undergo attempted stem cell mobilization will not be evaluable for the primary objective and will be replaced.

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 30-day follow up after the conclusion of treatment or death.

All patients are evaluable for disease response unless they discontinue treatment prior to completion of Cycle 2 and have not had any disease assessment.

5.5 General Concomitant Medication and Supportive Care Guidelines

Supportive care for prevention of tumor lysis syndrome (hydration, monitoring, etc.) must be performed per local institutional guidelines. Additional supportive care (e.g. transfusions, prophylactic antibiotics, antifungals and/or antivirals) is also allowed per institutional guidelines.

Use of growth factor is required for cycles 4-6. Growth factors may be initiated during cycles 1-3 at the discretion of the treating physician per institutional guidelines.

Prophylactic antiviral medications are obligatory during each cycle. Prophylactic antifungals are optional and may be administered at the discretion of the treating physician. PJP prophylaxis is optional and may be administered at the discretion of the treating physician. Autologous stem cell transplantation and post-transplant supportive care are not part of this study and will be undertaken per institutional standard and at the investigator's discretion.

Co-administration of corticosteroids and corticosteroid-containing eye drops (or equivalent) is recommended for patients receiving cytarabine-containing regimens. Eye drops should continue for at least 2 days following the last dose of cytarabine.

Antiemetic prophylaxis given per institutional guidelines is recommended.

Allopurinol should be used with caution along with bendamustine in view of potentially dangerous drug interactions.

Management of infusion reactions to rituximab and/or bendamustine will be undertaken as per institutional guidelines/standard of care.

5.5.1 Prohibited or Restricted Concomitant Therapy

In addition to the exclusion criteria:
The concomitant use of strong inhibitors/inducers of CYP3A4 (see Appendix D) should be avoided when possible. If a subject requires a strong CYP3A inhibitor while on study, monitor the subject closely for potential toxicities.

Acalabrutinib is not a strong direct inhibitor or inducer or CYP isoforms; thus, acalabrutinib, at the currently used clinical doses, is unlikely to be a perpetrator of a drug drug interaction at the level of inhibition or induction of CYP isoforms. Acalabrutinib is partially metabolized by CYP3A; its exposure is affected when co-administered with strong CYP3A4 inducers or inhibitors. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A4 (see Appendix D) should be avoided when possible.

If medically justified, subjects may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect these enzymes can be substituted within 7 days before first dose of study drug. If a subject requires a strong CYP3A4 while on study, monitor the subject closely for potential drug-related toxicities.

The effect of agents that reduce gastric acidity (antacids or proton pump inhibitors) on acalabrutinib absorption was evaluated in a healthy volunteer study. Results from this study indicate that subjects should avoid the use of calcium carbonate containing drugs or supplements for a period of at least 2 hours before and 2 hours after taking acalabrutinib. Use of omeprazole, esomeprazole, lansoprazole or any other proton pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. Although the effect of H2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose.

5.6 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum pregnancy test within 14 days prior to the first dose of study treatment.

Female and male patients (along with their female partners) are required to use highly effective contraception (defined as methods with failure rate < 1% per year) during participation in the study and for 12 months after last dose of any study drug.

If a patient is suspected to be pregnant, the study drugs should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within one month after the last dose of study treatment, the investigator must be notified in order to facilitate outcome follow-up.

5.7 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for 6 cycles or until one of the following criteria applies:

- Documented and confirmed disease progression based on PET imaging
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.8 Duration of Follow-up

Refer to Section 7.6 for adverse assessment timeframe.

Patients who have had a response to treatment will be followed clinically as part of routine care for 5 years or until death, whichever occurs first. Clinical follow-up frequency will be dictated per investigator's discretion, as per institutional standards. Data pertaining to PFS and OS will be collected from the medical record every 6 months for 5 years from study entry. Patients will initially be followed for disease status and development of any new malignancies. If a patient has progressive disease during the 5-year period, s/he will thereafter be followed only for survival.

Patients stopping protocol therapy early for any reason will be followed for disease status by review of the patient's medical record every 6 months for 5 years from study entry until progressive disease or initiation of alternative therapy, whichever occurs first, at which point the patient will be followed for survival.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

Subjects should be followed closely for AEs or laboratory abnormalities that might indicate treatment-related toxicity. If a subject experiences a treatment-related toxicity or other intolerable AE during the course of therapy, the treatment will be held or modified as described in the next paragraphs.

6.1 Criteria for Initiating a New Cycle

A new course of treatment may begin on the scheduled Day 1 of a new cycle if

- ANC $\geq$ 1000 (unless neutropenia is due to splenomegaly or marrow involvement by MCL).
- Platelets$\geq$100,000 (unless thrombocytopenia is due to splenomegaly or marrow involvement by MCL).
- Any non-hematologic grade 3 or 4 AE that is considered at least possibly related to chemotherapy has resolved to Grade 1 or lower.

6.2 Guidelines for Dose Modification and Discontinuation for Acalabrutinib

Agent	Starting Dose	Dose Level -1	Dose Level -2
Acalabrutinib	100mg BID	100mg QD	Discontinue

The actions in the table below should be followed for the following drug-related toxicities:

- Grade 3 or 4 thrombocytopenia in presence of significant bleeding regardless of marrow involvement.
- Grade 4 neutropenia lasting longer than 7 days
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy.
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity.

6.2.1 Drug Modification Actions for Acalabrutinib during BR and CR cycles

Occurrence	Action
1st	Hold acalabrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level.
2nd	Hold acalabrutinib until recovery to Grade≤1 or baseline; restart at one dose level lower (100mg QD).
3rd	For non-hematologic AEs, discontinue acalabrutinib.

	For thrombocytopenia with significant bleeding, discontinue acalabrutinib. For other hematologic AEs, hold acalabrutinib until recovery to Grade ≤1 or baseline; restart at one dose level lower (100 mg QD).
4th	For hematologic AEs, discontinue acalabrutinib.

Acalabrutinib may be held for a maximum of 28 consecutive days from expected dose due to toxicity. During this period, appropriate laboratory monitoring should be performed per institutional guidelines.

Acalabrutinib should be discontinued in the event of a grade 3 or 4 toxicity considered at least possibly related lasting > 28 days.

If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of acalabrutinib for ≥ 4 weeks then the dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment-related. Any changes to the dosing regimen must be recorded in the case report forms.

Acalabrutinib will be held if infusions of rituximab/bendamustine or rituximab/cytarabine are being held due to not meeting treatment parameters. Acalabrutinib will be restarted once these infusions are restarted in order to begin treatment cycles on the same day.

6.3 Guidelines for Dose Modifications and Discontinuation for Bendamustine / Rituximab (Cycles 1-3).

The following dose modifications should be made for grade 4 febrile neutropenia or cytopenias discovered on Day 1 of each cycle. Once reduced, dose levels may not be escalated. Of note, rituximab does not require dose reduction for cytopenias or life threatening febrile neutropenia.

For AE following bendamustine/rituximab cycles: dose decrease for the next bendamustine containing cycles (Cycles 2-3). A patient who requires a dose decrease of bendamustine will automatically require a dose decrease for the cytarabine containing cycles (cycles 4-6) as detailed below under 6.4.

Agent	Starting Dose	Dose Level -1	Dose Level -2
Bendamustine	90 mg/m^2	70 mg/m^2	50 mg/m^2

6.3.1 Neutropenia

- For ANC < 1000/mcl on the scheduled Day 1 of each cycle, delay bendamustine/rituximab treatment (unless neutropenia is due to marrow involvement by MCL) and follow CBC weekly until ANC ≥ 1000/mcl.
- For patients not receiving G-CSF with the previous bendamustine/rixutimab cycle, initiate filgrastim or pegfilgrastim for all subsequent cycles. No dose reduction for subsequent cycles is required if no growth factor was utilized in previous cycle.
- For patients receiving G-CSF with the previous bendamustine/rituximab cycle, if ANC recovers to ≥ 1000/mcl within 3 weeks of the scheduled Day 1, resume treatment. One dose level reduction will be used for the next bendamustine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated. Patients who require a dose decrease of bendamustine will also require a dose decrease for cytarabine/rituximab cycles (Cycles 4-6).
- There are no dose reductions below dose level -2. If dose reduction below dose level -2 is required for neutropenia, discontinue all protocol therapy.
- If any patient requires treatment delay > 21 days for persistent neutropenia despite optimal G-CSF usage, the patient will be removed from the study.

6.3.2 Thrombocytopenia

- For platelets <100,000/mcl on the scheduled Day 1 of each cycle, delay bendamustine/rituximab treatment (unless thrombocytopenia is due to marrow involvement by MCL) and follow CBC weekly until platelets ≥ 100,000/mcl.
- If platelets recover to ≥ 100,000/mcl within 21 days, resume bendamustine/rituximab treatment. One dose level reduction will be used for the next bendamustine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated. Patients who require a dose decrease of bendamustine will also require a dose decrease for cytarabine/rituximab cycles (Cycles 4-6).
- If any patient requires treatment delay > 21 days, the patient will be removed from the study.
- There are no dose reductions below dose level -2. If dose reduction below dose level -2 is required for thrombocytopenia, discontinue all protocol therapy.

6.3.3 CTCAE Grade 4 febrile neutropenia

- For CTCAE Grade 4 febrile neutropenia which has resolved in time for next cycle, resume bendamustine/rituximab treatment. One dose level reduction will be used for the next bendamustine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated. Patients who require a dose decrease of bendamustine will also require a dose decrease for cytarabine/rituximab cycles (Cycles 4-6).
- For CTCAE Grade 4 febrile neutropenia that has not resolved, hold bendamustine/rituximab until fever resolves and ANC is >1000, and then resume treatment. One dose level reduction will be used for the next

bendamustine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated. Patients who require a dose decrease of bendamustine will also require a dose decrease for cytarabine/rituximab cycles (Cycles 4-6).

- If patient experiences CTCAE Grade 4 febrile neutropenia at dose level -2, protocol therapy should be discontinued.
- Grade 3 febrile neutropenia does not require dose reductions in chemotherapy.

6.3.4 Non-Infectious Non-hematologic toxicity

- For grade 3-4 non-hematologic toxicity not related to an infection that is considered at least possibly, probably, or definitely related to chemotherapy, hold bendamustine/rituximab therapy, and follow weekly until toxicity improves to grade 1 or less. Delay cycle up to 21 days for resolution of the adverse event. Contact the study chair for delays exceeding 21 days.
- Once the toxicity has resolved to grade 1 or less, resume bendamustine/rituximab treatment. One dose level reduction will be used for the next bendamustine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated. Patients who require a dose decrease of bendamustine will also require a dose decrease for cytarabine/rituximab cycles (Cycles 4-6).
- For infusion reactions attributable to rituximab, supportive care should be provided per institutional protocols. Rituximab can be continued without dose reduction.
- For Grade 3 or 4 skin reactions or infusion reaction/anaphylaxis at least possibly, probably or definitely attributable to bendamustine, bendamustine should be permanently discontinued and rituximab may be discontinued as well at the discretion of the treating physician.

6.3.5 Infectious non-hematologic Toxicity

- For CTCAE Grade 4 infection, that is considered at least possibly, probably, or definitely related to chemotherapy, which has resolved in time for next cycle, resume bendamustine/rituximab treatment. One dose level reduction will be used for the next bendamustine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated. Patients who require a dose decrease of bendamustine will also require a dose decrease for cytarabine/rituximab cycles (Cycles 4-6).
- For CTCAE Grade 4 infection that has not resolved, hold bendamustine/rituximab therapy until event resolves and ANC is >1000, and then resume treatment. One dose level reduction will be used for the next bendamustine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated. Patients who require a dose decrease of bendamustine will also require a dose decrease for cytarabine/rituximab cycles (Cycles 4-6).
- If patient experiences CTCAE Grade 4 infection at dose level -2, all protocol

therapy (including acalabrutinib) should be discontinued.

- Infections which are grade 1, 2 or 3 do not require holding or dose reducing chemotherapy.
- Rituximab should be discontinued in the following circumstances: progressive multifocal leukoencephalopathy (PML), significant vesicular or bullous dermatitis, or Stevens-Johnsons syndrome.

6.4 Guidelines for Dose Modifications and Discontinuation for Cytarabine / Rituximab (Cycles 4-6)

The following dose modifications should be made for grade 4 febrile neutropenia or cytopenias discovered on Day 1 of each cycle. Once reduced, dose levels may not be escalated. Of note, rituximab does not require dose reduction for cytopenias or life threatening febrile neutropenia.

For AE following cytarabine/rituximab cycles: dose decrease for the next Cytarabine containing cycles (Cycles 4-6).
Patients who required a dose decrease in bendamusine/rituximab cycles will automatically require a dose decrease for their cytarabine/rituximab cycles (begin at dose level -1).

Agent	Starting Dose	Dose Level -1	Dose Level -2
Cytarabine	$2g/m^2$ ($1.5\ g/m^2$ for patients 60-70)	$1.5\ g/m^2$ ($1.0\ g/m^2$ for patients 60-70)	$1\ g/m^2$ ($0.5\ g/m^2$ for patients 60-70)

6.4.1 Neutropenia

- For ANC < 1000/mcl on the scheduled Day 1 of each cycle, delay cytarabine/rituximab treatment (unless neutropenia is due to marrow involvement by MCL) and follow CBC weekly until ANC ≥ 1000/mcl.
- For patients not receiving G-CSF with the previous cytarabine/rituximab cycle, initiate filgrastim or pegfilgrastim for all subsequent cycles. No dose reduction for subsequent cycles is required if no growth factor was utilized in previous cycle.
- For patients receiving G-CSF with the previous cytarabine/rituximab cycle, if ANC recovers to ≥ 1000/mcl within 3 weeks of the scheduled Day 1, resume cytarabine/rituximab treatment. One dose level reduction will be used for the next cytarabine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated.
- There are no dose reductions below dose level -2. If dose reduction below dose level -2 is required for neutropenia, discontinue all protocol therapy (including acalabrutinib).
- If any patient requires treatment delay > 21 days for persistent neutropenia despite optimal G-CSF usage, the patient will be removed from the study.

6.4.2 Thrombocytopenia

- For platelets <100,000/mcl on the scheduled Day 1 of each cycle, delay cytarabine/rituximab treatment (unless thrombocytopenia is due to marrow involvement by MCL) and follow CBC weekly until platelets ≥ 100,000/mcl.
- If platelets recover to ≥ 100,000/mcl within 21 days, resume cytarabine/rituximab treatment. One dose level reduction will be used for the next cytarabine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated.
- If any patient requires treatment delay > 21 days, the patient will be removed from the study.
- There are no dose reductions below dose level -2. If dose reduction below dose level -2 is required for thrombocytopenia, discontinue all protocol therapy (including acalabrutinib).

6.4.3 CTCAE Grade 4 febrile neutropenia

- For CTCAE Grade 4 febrile neutropenia which has resolved in time for next cycle, resume cytarabine/rituximab treatment. One dose level reduction will be used for the next cytarabine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated.
- For CTCAE Grade 4 febrile neutropenia that has not resolved, hold cytarabine/rituximab therapy until fever resolves and ANC is >1000, and then resume cytarabine/rituximab treatment. One dose level reduction will be used for the next cytarabine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated. If patient experiences CTCAE Grade 4 febrile neutropenia at dose level -2, all protocol therapy (including acalabrutinib) should be discontinued.
- Grade 3 febrile neutropenia does not require dose reductions in chemotherapy.

6.4.4 Non-Infectious Non-hematologic toxicity

- For grade 3-4 non-hematologic toxicity not related to an infection that is considered at least possibly, probably, or definitely related to chemotherapy, hold cytarabine/rituximab therapy, and follow weekly until toxicity improves to grade 1 or less. Delay cycle up to 21 days for resolution of the adverse event. Contact the study chair for delays exceeding 21 days.
- Once the toxicity has resolved to grade 1 or less, resume cytarabine/rituximab treatment. One dose level reduction will be used for the next cytarabine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated.
- For infusion reactions attributable to rituximab, supportive care should be provided per institutional protocols. Rituximab can be continued without dose reduction.

6.4.5 Infectious non-hematologic Toxicity

- For CTCAE Grade 4 infection, that is considered at least possibly, probably, or definitely related to chemotherapy, which has resolved in time for next cycle, resume cytarabine/rituximab treatment. One dose level reduction will be used for the next cytarabine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated.
- For CTCAE Grade 4 infection that has not resolved, hold cytarabine/rituximab therapy until event resolves and ANC is >1000, and then resume cytarabine/rituximab treatment. One dose level reduction will be used for the next cytarabine/rituximab cycle. All subsequent cycles will proceed at the reduced dose, which may not be re-escalated.
- If patient experiences CTCAE Grade 4 infection at dose level -2, all protocol therapy should be discontinued (including acalabrutinib).
- Infections which are grade 1, 2 or 3 do not require holding or dose reducing chemotherapy.
- Rituximab should be discontinued in the following circumstances: progressive multifocal leukoencephalopathy (PML), significant vesicular or bullous dermatitis, or Stevens-Johnsons syndrome.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2.

The FDA requires that all serious and unexpected adverse events be reported as outlined in Section 7.5. In addition, any fatal or life-threatening adverse experiences where there is a reasonable possibility of relationship to study intervention must be reported.

Acerta requires that all events be reported as outlined in Section 7.4.

7.1 Definitions

7.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

7.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

All unexpected SAEs must be reported to the FDA.

7.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

Events that are both serious AND unexpected must be reported to the FDA.

7.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Life-threatening adverse experiences must be reported to the FDA.

7.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b)

the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

7.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the

event or notification to the PI of the event.

7.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

7.4 Reporting to AstraZeneca

All SAEs must be reported to AstraZeneca within 7 days of discovery for fatal and life-threatening reports (15 days for other SAE and special situation reports) and to the IRB. AstraZeneca Pharma may request follow-up and other additional information from the investigator.

Whenever possible, SAEs should be reported by diagnosis term; not as a constellation of symptoms. All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product and is not listed in the current Investigator Brochure (ie, an unexpected event).

Drug Safety Contact Information
AZ Patient Safety - TCS
Fax: 1-302-886-4114
Email: AEMailboxClinicalTrialTCS@astrazeneca.com

7.5 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences (Section 7.1.4)

associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than **7 calendar days** after initial receipt of the information.

- Report any serious, unexpected adverse experiences (Section 7.1.2), as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information.

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

7.6 Timeframe for Reporting Required Events

Adverse events will be tracked from start of treatment until 30 days after the last dose of study treatment regardless of the start of subsequent treatment for MCL. AE assessment may be done by phone call or in-person visit. Beyond this timeframe, if the investigator becomes aware of any SAEs or deaths that are assessed as related to acalabrutinib, they must be reported to Acerta as described in Section 7.4.

8.0 PHARMACEUTICAL INFORMATION

8.1 Acalabrutinib

8.1.1 Acalabrutinib Description

Chemical Name: 4-{8-amino-3-[(2S)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(pyridin-2-yl)benzamide
Molecular formula: C26H23N7O2
Molecular weight: 465.517 g/mol
Pharmacologic class: Small molecule.

8.1.2 Clinical Pharmacology

Acalabrutinib is a small-molecule inhibitor of BTK. Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies,

acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and survival.

In patients with B-cell malignancies dosed with 100 mg twice daily, median steady state BTK occupancy of ≥ 95% in peripheral blood was maintained over 12 hours, resulting in inactivation of BTK throughout the recommended dosing interval.

8.1.3 Pharmacokinetics and Drug Metabolism

The pharmacokinetics (PK) of acalabrutinib was studied in healthy subjects and patients with B-cell malignancies. Acalabrutinib exhibits almost linear PK across a dose range of 75 to 250 mg (0.75 to 2.5 times the approved recommended single dose) and exhibits dose-proportionality. The daily area under the plasma drug concentration over time curve (AUC) was 1111 ng•h/mL and maximum plasma concentration (Cmax) of acalabrutinib was 323 ng/mL.

Absorption
The geometric mean absolute bioavailability of acalabrutinib was 25%. Median time to peak acalabrutinib plasma concentrations (Tmax) was 0.75 hours.

Effect of Food
In healthy subjects, administration of a single 75 mg dose of acalabrutinib (0.75 times the approved recommended single dose) with a high-fat, high-calorie meal (approximately 918 calories, 59 grams carbohydrate, 59 grams fat, and 39 grams protein) did not affect the mean AUC as compared to dosing under fasted conditions. Resulting Cmax decreased by 73% and Tmax was delayed 1-2 hours.

Distribution
Reversible binding of acalabrutinib to human plasma protein was 97.5%. The in vitro mean blood-to plasma ratio was 0.7. The mean steady-state volume of distribution (Vss) was approximately 34 L.

Elimination
Following a single oral dose of 100 mg acalabrutinib, the median terminal elimination half-life (t1/2) of acalabrutinib was 0.9 (range: 0.6 to 2.8) hours. The t1/2 of the active metabolite, ACP-5862, was 6.9 hours. Acalabrutinib mean apparent oral clearance (CL/F) was 159 L/hr with similar PK between patients and healthy subjects, based on population PK analysis.

Metabolism
Acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent, by glutathione conjugation and amide hydrolysis, based on in vitro studies. ACP-5862 was identified as the major active metabolite in plasma with a geometric mean exposure (AUC) that was approximately 2- to 3-fold higher than the exposure of acalabrutinib. ACP-5862 is approximately 50% less potent than acalabrutinib with regard to BTK inhibition.

Excretion
Following administration of a single 100 mg radiolabeled acalabrutinib dose in healthy subjects, 84% of the dose was recovered in the feces and 12% of the dose was recovered in the urine, with less than 1% of the dose excreted as unchanged acalabrutinib.

Specific Populations
Age, Race, and Body Weight
Age (42 to 90 years), sex, race (Caucasian, African American), and body weight did not have clinically meaningful effects on the PK of acalabrutinib, based on population PK analysis.

Renal Impairment
Acalabrutinib undergoes minimal renal elimination. Based on population PK analysis, no clinically relevant PK difference was observed in 368 patients with mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73m2, as estimated by MDRD (modification of diet in renal disease equation)). Acalabrutinib PK has not been evaluated in patients with severe renal impairment (eGFR < 29 mL/min/1.73m2, MDRD) or renal impairment requiring dialysis.

Hepatic Impairment
Acalabrutinib is metabolized in the liver. In a hepatic impairment study, compared to subjects with normal liver function (n=6), acalabrutinib exposure (AUC) was increased by less than two-fold in subjects with mild (n=6) (Child-Pugh A) and moderate (n=6) (Child-Pugh B) hepatic impairment, respectively. Based on a population PK analysis, no clinically relevant PK difference was observed in subjects with mild (n=41) or moderate (n=3) hepatic impairment (total bilirubin between 1.5 to 3 times the upper limit of normal [ULN] and any AST) relative to subjects with normal (n=527) hepatic function (total bilirubin and AST within ULN). Acalabrutinib PK has not been evaluated in patients with severe hepatic impairment (Child-Pugh C or total bilirubin between 3 and 10 times ULN and any AST).

8.1.4 Supplier(s)

Acalabrutinib capsules for this trial will be supplied by AstraZeneca.

8.1.5 Dosage Form and Preparation

Acalabrutinib capsules for oral administration are supplied as yellow and blue, opaque hard gelatin capsules, with 100 mg of acalabrutinib as the active ingredient. Each capsule also contains compendial inactive ingredients: silicified microcrystalline cellulose, which is composed of microcrystalline cellulose and colloidal silicon dioxide, partially pregelatinized starch, sodium starch glycolate, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide,

yellow iron oxide and indigotine (FD&C Blue 2).

Acalabrutinib will be provided in white, high-density polyethylene bottles.

8.1.6 Storage and Stability

Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F).

8.1.7 Administration

Acalabrutinib 100mg BID administered orally Days 1-28 of Cycles 1, 3, and 5 and Days 1-7 and 22-28 of Cycles 2, 4, and 6.

8.2 Cytosine Arabinoside

8.2.1 Cytosine Arabinoside Description

Chemical Name: 4-amino-1-S-D-arabino-furanosyl-2(1H)-primidinone
Molecular formula: C9H13N3O5
Molecular weight: 243.217g/mol
Pharmacologic class: Antimetabolite

8.2.2 Clinical Pharmacology

Cytarabine is metabolized to its active form, cytarabine triphosphate (AraCTP) by deoxycytidine kinase and related kinases. AraCTP serves as an inhibitor of DNA polymerase. AraC also is incorporated into cellular RNA and DNA. It exhibits cell phase specificity, and is active against cells in the S-phase and may also block cells from progressing to S phase from G1.

8.2.3 Pharmacokinetics and Drug Metabolism

After intravenous administration, the disappearance of Cytarabine from plasma is biphasic. There is an initial distributive phase with a half-life of approximately 10 minutes, followed by a second elimination phase with a half-life of approximately 1 to 3 hours. Within 24 hours about 80 percent of the administered drug can be recovered in the urine as the inactive metabolite, AraI. After a single IV administration of Cytarabine, levels in CSF are low. There is little conversion to AraU because of low CSF levels of diaminase.

8.2.4 Supplier(s)

Cytarabine is commercially available and will be supplied by the treating institution.

8.2.5 Dosage Form and Preparation

Cytarabine is supplied as a sterile powder in 100 mg, 500 mg, 1 gram, and 2 gram vials for injection. Cytarabine should be reconstituted with sterile water for injection. Please refer to the package insert for further instructions.

8.2.6 Storage and Stability

Sterile powder should be stored at room temperature 15° -30°C (59°- 86°F). Solutions reconstituted with sterile water without preservative should be used immediately; solutions reconstituted with Bacteriostatic of Water are stable up to 48 hours at room temperature 15° -30°C (59°- 86°F). Solutions with a slight haze should be discarded.

8.2.7 Administration

Cytarabine 2 g/m^2 every 12 hours for 4 doses by intravenous infusion over 2 hours. Patients 60-70 years will receive 1.5 g/m^2.

8.3 Rituximab

8.3.1 Rituximab Description

Other Names: IDEC-C2B8, Chimeric anti-CD20 monoclonal antibody, Rituxan, NSC# 687451
Classification: Monoclonal Antibody

8.3.2 Clinical Pharmacology

Rituximab is a chimeric murine/human gamma 1 kappa monoclonal antibody (Chinese hamster ovary [CHO] transfectoma). It recognizes the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas. It binds with high affinity to CD20-positive cells, performs human effector functions in vitro, and depletes B-cells in vivo. The Fab domain of Rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis in vitro. The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow.

8.3.3 Pharmacokinetics and Drug Metabolism

Rituximab may be detectable in serum up to 3-6 months after infusion. B cell recovery commences approximately 6 months after completion of treatment with median recovery time of 12 months. Intravenous administration results in rapid and sustained tissue and circulating B cell depletion. Its elimination is uncertain but thought to be through catabolism in the reticuloendothelial system with a t1/2 of 22 days (range 6-52 days)

8.3.4 Supplier(s)

Rituximab is commercially available will be supplied by the treating institution.

8.3.5 Dosage Form and Preparation

Rituximab will be diluted with 0.9% Sodium Chloride or 5% Dextrose Injection to prepare a standard product with concentration of 2 mg/ml. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody

8.3.6 Storage and Stability

Vials should be protected from direct sunlight. Diluted drug product at a concentration of 1 to 4 mg/ml in polyvinylchloride or polyolefin IV bags containing normal saline or dextrose 5% can be stored for up to 24 hours at 2 to 8˚C, and at room temperature for an additional 24 hours.

8.3.7 Administration

Rituximab will be administered as an intravenous infusion at 375 mg/m2 on Day 1 of each cycle (or on Day 2 of Cycle 1). The first dose of rituximab should be infused at 50 mg/hour and the rate of infusion increased by 50 mg/hour gradually to a rate of 400 mg/hour. Subsequent doses may be administered at 100 mg/hour over 30 minutes. The remainder of the dose may be administered over 60 minutes. During rituximab infusion, a patient's vital signs (blood pressure, pulse, respiration, temperature) should be monitored according to the standard of care.

8.4 Bendamustine

8.4.1 Bendamustine Description

Classification: Alkylating agent

8.4.2 Clinical pharmacology

Bendamustine is a nitrogen mustard derivative with a benzimidazole ring (purine analog) which demonstrates only partial cross-resistance (in vitro) with other alkylating agents. It leads to cell death via single and double strand DNA cross-linking. Bendamustine is active against quiescent and dividing cells. The primary cytotoxic activity is due to bendamustine (as compared to metabolites).

8.4.3 Pharmacokinetics and Drug Metabolism

Bendamustine is highly protein bound (94-96%) It is extensively hepatically

metabolized via CYP1A2 to active (minor) metabolites gamma-hydroxybendamustine (M3) and N-desmethyl-bendamustine (M4); also via hydrolysis to low cytotoxic metabolites, monohydroxybendamustine (HP1) and dihydroxybendamustine (HP2). The elimination t1/2 of bendamustine (the cardinal active agent) is ~40 minutes. The elimination t1/2of M3 is ~3 hours and M4 is about 30 minutes. Bendamustine is excreted through urine (50%, 3% as active drug) and feces (25%)

8.4.4 Supplier(s)

Bendamustine is commercially available and will be supplied by the treating institution

8.4.5 Dosage Form and Preparation

Bendamustine is supplied in a multi-dose vial at a concentration of 100 mg/4mL vial (25 mg/mL). Aseptically withdraw the volume needed for the required dose and immediately transfer into a 50 mL infusion bag containing 0.9% NS or 5% dextrose or 2.5% dextrose/0.45% sodium chloride.

8.4.6 Storage and Stability

Intact vials should be stored at room temperature and protected from light. Once reconstituted or further diluted for infusion, bendamustine is stable for 24 hours when stored refrigerated (2-8°C or 36-47°C) or for 6hours when stored at room temperature (15-30°C or 59-86°F) and room light.

8.4.7 Administration

Bendamustine is infused at a dose of 90 mg/m^2 over 30 minutes and is an irritant with vesicant like properties. Bendamustine solution contains N, N-dimethylacetamide, which is incompatible with closed-system transfer devices (CSTDs), adapters, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene (ABS). After dilution of bendamustine solution into the infusion bag, devices containing polycarbonate or ABS (including infusion sets) may be used.

9.0 CORRELATIVE STUDIES

Correlative studies will include evaluating the genomic alterations, immune cell composition, and minimal residual disease (MRD) prior to, during, and at the end of treatment.

9.1 Lymphoma Tissue Collection

Lymphoma tissue will be collected for defining baseline genomic alterations for correlation

with clinical outcomes and to provide a baseline for the lymphoma clones that will be monitored in follow-up samples (MRD tests).

This assay will be performed by the Fehniger Lab at WUSM. A fresh/frozen or formalin-fixed paraffin embedded (FFPE) tissue block that includes the patient's iNHL, other MCL involved tissue, or bone marrow aspirate.

Genomic DNA will be isolated and analyzed for recurrent mutations via next-generation sequencing. While fresh/frozen tissue is not required, it is greatly preferred over FFPE tissue blocks. A biopsy specimen obtained immediately prior to the start of study treatment is preferred, as this reflects the tumor genomic content at time of entering the study. If the FFPE tissue block is not available, 10 unstained slides or ribbons sufficient to isolate 10 mcg of gDNA may be substituted.

9.2 Non-Malignant Oral Rinse Collection

An oral rinse will be performed to obtain an additional non-tumor cellular sample (Oragene –discover DNA genotek) in order to define baseline genomic alterations for correlation with clinical outcomes and to provide a baseline for the lymphoma clones that will be monitored in follow-up samples (MRD tests).

Genomic DNA will be isolated and analyzed for recurrent mutations via next-generation sequencing.

9.3 Peripheral Blood Collection

Peripheral blood will be collected for the MRD test and immune monitoring at the following time points:

- Baseline
- End of Cycle 3
- 4-6 weeks after Cycle 6 Day 1
- If the patient discontinues protocol therapy prior to completion of Cycle 6

Peripheral blood will be collected in two 10-mL pink top EDTA tubes and two 10-mL green top heparin tubes (total of 4 tubes). Pink top tubes will be used to generate plasma for cfDNA MRD testing. Green top tubes will be used to isolate immune cells for immunomonitoring.

9.4 Bone Marrow Collection

Bone marrow will be collected at baseline if the patient requires a marrow for staging purposes and has not already had a bone marrow biopsy performed. Bone marrow will also be collected at end of treatment if the patient requires a marrow for restaging. At each time point, 2-5 mL of bone marrow aspirate should be collected in a 10-mL pink top EDTA tube.

9.5 Sample Storage

All samples should be submitted to the Fehniger Lab Monday through Friday 8 am until 5 pm:

Attention: Fehniger Lab / Michelle Hapak
Fehniger Lab 7
Southwest Tower Building
Room 724
4940 Parkview Place
St Louis MO 63110
Phone: 314-273-0156 or 314-747-1547
Email: mbecker-hapak@wustl.edu; tfehnige@wustl.edu

10.0 STUDY CALENDAR

Screening/baseline evaluations are to be conducted within 28 days prior to start of protocol therapy. There is a +/- 3 day window for tests, observations, labs, and/or treatment.

Tests and observations	Baseline examination[1]	Treatment phase[2]	EOT[17]	Follow-up[3]
Informed consent	X			
Physical exam	X	X		
Medical history	X			
Medication Review[18]	X	**X**		
Performance status	X			
Toxicity assessment[4]	X	X	X[15]	
Pill diary		X		
Review of medical record for progression and survival				X
Laboratory Studies				
CBC with differential[5]	X	X		
CMP[6]	X	X		
Uric acid	X	X		
LDH	X	X		
Serum pregnancy test [7]	X			
HIV-1/2 antibody	X			
Hepatitis B surface antigen, surface antibody, and core antibody[8]	X			
Hepatitis C antibody[9]	X			
MIPI score[10]	X			
PET[11]	X	X	X	
Bone marrow aspiration and biopsy[12]	X	X	X	
EKG	X			
Correlative Studies				
Ki-67 (WU pathology review)[13]	X			
Blood for immune biomarkers[14]	X	X	X	
Lymphoma tissue for genomic alterations and MRD assessment	X			
Oral rinse	X			
Blood for MRD assessment[14]	X	X	X	
Bone marrow aspiration for research[16]	X	X[12]		

Notes:

1. All baseline examinations are to be performed within 28 days of the start of therapy
2. Treatment phase begins with first dose of acalabrutinib (Day 1). Tests, observations, and laboratory studies will be performed on Day 1 of each cycle.
3. The frequency of follow-up after completion of protocol treatment is per investigator's discretion. Review of the medical record will occur on an every 6-month basis for 5 years from study entry to collect data on relapse and survival.
4. Only toxicities which worsen from baseline need be collected, and only the worst grade per cycle need be recorded. Toxicity will be assessed from time of treatment initiation until the end-of-study restaging visit, approximately one month after the last dose of chemotherapy.
5. CBC with differential will be performed on Day 1 each cycle. On cycles 1, 3, and 5 the CBC will be repeated between day 10 and day 14. On cycles 2, 4, and 6 the CBC will be repeated at least twice between days 8-14 and twice between days 15-21.
6. CMP will be performed during screening and on Day 1 of each cycle
7. For women of child bearing potential. Perform within 14 days of study entry.
8. Subjects who are hepatitis B core antibody positive but surface antigen negative will need negative polymerase chain reaction (PCR) prior to enrollment. Hepatitis B surface antigen positive or PCR positive patients are ineligible.
9. Subjects who are hepatitis C antibody positive will need negative PCR prior to enrollment. Patients with PCR positive hepatitis C are ineligible.
10. The mantle cell IPI (MIPI) calculator can be accessed at http://www.european-mcl.net/en/clinical_mipi.php
11. PET scans are required for every restaging scan while on protocol. PET scans will be performed at baseline, after Cycle 3, and after Cycle 6. Patients who come off treatment early for reasons other than progression who are suspected to be responders should have an EOT assessment with PET imaging.
12. Bone marrow aspirate will be collected at baseline if the patient has not already had a bone marrow biopsy performed prior to enrolling to the study. If marrow is involved at baseline, repeat bone marrow aspiration and biopsy is required after 6 cycles of chemotherapy. Patients who come off treatment early for reasons other than progression who are suspected to be responders should have an EOT bone marrow aspiration and biopsy if they had a baseline assessment.
13. Pathology review of the patient's baseline diagnostic tissue, including lymph node, bone marrow biopsy, or blood, will include an immunohistochemical assessment of Ki-67. If the Ki-67 is already available in the WU pathology report at time of screening, the test does not need to be repeated. The result is not required at the time of patient enrollment.
14. Peripheral blood will be collected at baseline, end of Cycle 3, 4-6 weeks after Cycle 6 Day 1, and at discontinuation of treatment (if prior to Cycle 6). See Section 9.0.
15. Adverse events will be tracked for 30 days after the last dose of study treatment. Refer to Section 7.6 for details. If the investigator becomes aware of any SAEs or deaths that are causally attributed to acalabrutinib after the 30-day time period, they must be reported to AstraZeneca.
16. Only if required clinically.
17. End of treatment visit will take place 4-6 weeks after Cycle 6 Day 1.
18. Medication review at baseline and at Day 1 of each cycle to verify that patients is not taking PPIs or CYP3A4 inhibitor/inducers.

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Lymph Node Tumor Biopsy Form Bone Marrow Biopsy Form (if applicable) MRD Testing Form Research Blood Form	Prior to starting treatment
Treatment Form	Every cycle
Disease Assessment Form	Baseline, and after Cycles 3 and 6 at restaging
Research Blood Form MRD Testing Form	End of Cycle 3 4-6 weeks after Cycle 6 Day 1
Treatment Summary Form Leukapheresis and Transplant Form Bone Marrow Biopsy Form (if applicable) MRD Testing Form (if applicable) Research Blood Form (if applicable)	Completion of treatment
Disease Status Follow-Up Form	Every 6 months for 5 years after study entry until the patient's first relapse. After a patient has disease progression within the 5-year period, switch to the Survival Follow-Up Form.
Survival Follow-Up Form	Beginning from patient's first relapse, every 6 months for 5 years after study entry
Adverse Event Form	Baseline, and at the time of any toxicity from starting treatment to one month after completing treatment
MedWatch Form	See Section 7.0 for reporting requirements
Death Form	Time of death

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect

For the purposes of this study, patients should be re-evaluated for response after 3 and 6 cycles of therapy while on treatment with PET imaging.

12.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. PET based evaluation is required over evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

12.3 Criteria for extranodal involvement(18)

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Focal uptake in extranodal sites that is in keeping with lymphoma, according to the distribution and/or CT characteristics, is considered involvement with lymphoma, including spleen, liver, bone, thyroid, skin, lung, and bone marrow. A measurable extranodal lesion should have a longest diameter greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (e.g. cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

12.4 Response Assessment

Response to treatment is guided based upon the Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification.[18]PET restaging scans will be performed after Cycle 3 and Cycle 6, then as clinically indicated.

Tissue site	Clinical	Test	Positive finding
Lymph node	Palpable	PET/CT	Increased FDG avidity
Spleen	Palpable	PET/CT	Diffuse uptake, solitary mass, miliary lesions, nodules
Liver	Palpable	PET/CT	Diffuse uptake, mass
CNS	Signs, symptoms	CSF (if clinically indicated)	Cytology, flow cytometry
Other (e.g. skin, lung, GU tract, bone, marrow)	Site dependent	PET/CT	Biopsy, if clinically indicated

12.4.1 Complete Response (CR)

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- London Deauville score of 1 and 2 in lymph nodes and extra lymphatic sites is

considered to represent complete metabolic response. A London Deauville score 3 in the post treatment PET scan may be considered to represent complete metabolic response especially if it is not higher than the surrounding normal physiologic uptake.

- No evidence of FDG avid disease in the bone marrow
- No new lesions
- If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

12.4.2 Partial Response (PR)

- London Deauville score of 4 or 5 in lymph nodes and extra lymphatic sites with reduced uptake compared with the baseline and residual mass(es) of any size on interim scan
- Residual bone marrow uptake higher than the uptake in the normal marrow but reduced when compared with baseline 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
- No new lesions

12.4.3 No Metabolic Response (SD)

- London Deauville score of 4 or 5 in target nodes/masses/extranodal lesions with no significant change in FDG uptake from baseline at interim or end of treatment
- No change in bone marrow from baseline
- No new lesions

12.4.4 Progressive Disease (PD)

- London Deauville score of 4 or 5 in individual target nodes/masses with an increase in intensity of uptake from the baseline and/or new FDG avid foci consistent with lymphoma at interim or end of treatment assessment
- New FDG avid foci of extranodal disease consistent with lymphoma. If there is concern regarding the etiology of the new lesions, biopsy or interval scan may be considered.
- New or recurrent FDG avid foci in the bone marrow

12.4.5 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least monthly and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Early study suspension rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

14.0 STATISTICAL CONSIDERATIONS

All patients who receive study treatment and undergo at least a single pheresis procedure with the aim of harvesting stem cells are evaluable for the primary objective. Patients who do not undergo

attempted stem cell collection due to disease progression, toxicity, patient preference, or discretion of the treating physician will be replaced.

Mobilization failure is expected to be 5% or less. Such a small amount is difficult to monitor statistically in a sample of 15 evaluable patients. Instead, the study will allow no more than 2 cases among 15 evaluable patients. The study will be suspended for review if the third case is observed. 95% confidence intervals for 0, 1 and 2 cases in 15 evaluable patients are (0.0, 0.22), (.0017, .32) and (.017, .40), respectively.

The study also will be suspended for review following the death of a patient during protocol defined treatment or within 30 days after the last dose of protocol treatment or until initiation of a new anti-cancer therapy (whichever is first). The study will not be suspended for review if a death was determined to be related to disease progression.

Treatment related non-hematologic toxicity of grade 3 or higher will be monitored using a continuous toxicity monitoring rule.

The expected rate is 30% and the maximum allowable rate is 60%. The toxicity monitoring rule has type 1 and 2 error rates of 0.05 and 0.20, respectively. The probability of incorrect study suspension is 0.059 if the true toxicity rate is 30%. The probability of correct study suspension is 0.70 if the true toxicity rate is as high as 60%.

Suspend the study for review if the number of patients with treatment related grade 3+ non hematologic toxicities EXCEEDS:	**In the following number of enrolled patients:**
2	3
3	4
4	6
5	9
6	11
7	13
8	15

Analysis Plan: Stem cell mobilization rate, ORR and CRR will be documented as proportions with exact binomial 95% confidence intervals. Kaplan-Meier method will be used to describe OS and PFS, as well as to estimate median times to these events with 95% confidence intervals if the median is reached. Adverse and serious adverse events will be tabulated by cycle, patient, type and grade.

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: PATIENT'S MEDICATION DIARY –CYCLES 1-3

Today's Date: _____ Study ID#: _____ Agent: Acalabrutinib Cycle: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take 100 mg of acalabrutinib twice daily (approximately 12 hours apart) with or without food. Take it with a glass of water and drink the glass of water in as little time as possible. Swallow the capsules whole and do not chew the capsules.
2. Record the date, the number of capsules taken, and when you took them.
3. If you forgot to take your acalabrutinib dose and it's been more than 3 hours since the regular dosing time, then do not take that dose. Restart taking it with the next scheduled dose.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.

Day	Date	What time was dose taken?		# of capsules taken		Comments
		AM dose	PM dose	AM dose	PM dose	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
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27						
28						

APPENDIX C: PATIENT'S MEDICATION DIARY –CYCLES 4-6

Today's Date: _____ Study ID#: _____ Agent: Acalabrutinib Cycle: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take 100 mg of acalabrutinib twice daily (approximately 12 hours apart) with or without food. Take it with a glass of water and drink the glass of water in as little time as possible. Swallow the capsules whole and do not chew the capsules.
2. Record the date, the number of capsules taken, and when you took them.
3. If you forgot to take your acalabrutinib dose and it's been more than 3 hours since the regular dosing time, then do not take that dose. Restart taking it with the next scheduled dose.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.

Day	Date	What time was dose taken?		# of capsules taken		Comments
		AM dose	PM dose	AM dose	PM dose	
1						
2						
3						
4						
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APPENDIX D: Known Strong in Vivo Inhibitors or Inducers of CYP3A

Strong Inhibitors of CYP3A[a]	Strong Inducers of CYP3A[e]
boceprevir	carbamazepine[f]
clarithromycin[b]	phenytoin[f]
conivaptin[b]	rifampin[f]
grapefruit juice[c]	St John's wort[f]
indinavir	
itraconazole[b]	
ketoconazole[b]	
lopinavir/ritonavir[b] (combination drug)	
mibefradil[d]	
nefazodone	
nelfinavir	
posaconazole	
ritonavir[b]	
saquinavir	
telaprevir	
telithromycin	
voriconazole	

a. A strong inhibitor for CYP3A is defined as an inhibitor that increases the AUC of a substrate for CYP3A by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).
d. Withdrawn from the United States market because of safety reasons.
e. A strong inducer for CYP3A is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate for CYP3A.
f. In vivo inducer of P-glycoprotein.

Note: The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the Medical Monitor of the protocol.

Source:

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers . Web link Accessed 11 June 2015:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo