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STUDY TITLE: **Phase II Study of Rituximab and Acalabrutinib in Newly Diagnosed B Cell Post Transplant Lymphoproliferative Disorder (PTLD)**

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SUPPLIED AGENT*:* Acalabrutinib

IND #: [redacted]

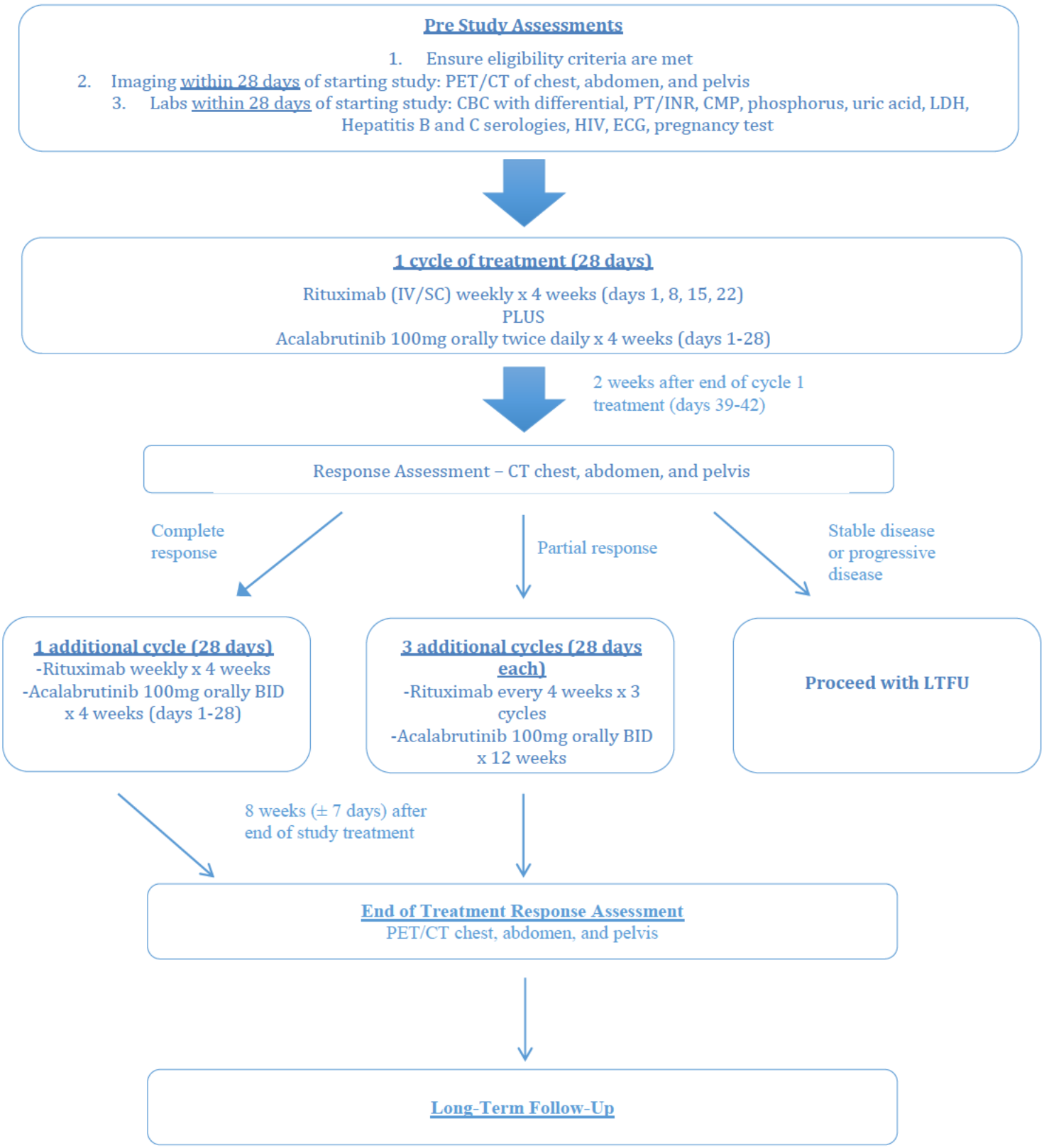
OTHER AGENT*:* Rituximab

SUMMARY OF CHANGES

Protocol Date	Section	Change
11/13/2019		Initial PRMC approval
4/3/2020	throughout	Minor formatting and grammatical updates
4/3/2020	1.1	Added some information to the background of PTLD
4/3/2020	4.1.1	Added the histological diagnoses of PTLD in the inclusion criteria per WHO 2016 criteria
4/3/2020	4.1.4; appendix 4	Added creatinine clearance eligibility criteria for renal function
4/3/2020	4.2.21 & 4.2.22	Revised the exclusion criteria to exclude patients with acute GVHD and/or transplant organ rejection
4/3/2020	6.1	Clarified that subjects are not required to fail the trial of immunosuppression prior to starting study treatment
4/3/2020	6.1.1	Added hematologic criteria required to initiate each treatment cycle
4/3/2020	6.4	Added the development of second primary malignancy to the criteria for removal from the study
4/3/2020	7.1	Revised the dose delay/modification criteria for acalabrutinib
4/3/2020	9.2	Clarified that rituximab administration should be done per local institutional standard of care
4/3/2020	10.0	Revised the instructions for specimen collection for correlative studies
4/3/2020	11.1.1; 11.1.2; 11.2; 12.0	Clarified that PET scan is preferred for patients is insurance only allows one type of scan and that the same radiologic imaging that was obtained at screening will be used to assess response
4/3/2020	11.1.1	Added that if baseline tissue is not available, approval from the sponsor-investigator is required to enroll
4/3/2020	14.4	Added toxicity monitoring rules
4/18/2020	Cover Page	Added NCT number
4/18/2020	Schema and throughout	Changed the Interim Response Assessment to take place during days 39-42 (instead of day 36 ± 5 days) and for cycle 2 to start within 2 weeks (instead of 3 weeks) of the end of cycle one treatment
4/18/2020	4.1.5	Added highly effective methods of contraception
4/18/2020	8.1.1.1	Updated the language for second primary malignancies and removed pregnancy and breastfeeding from the warning and precautions section
4/18/2020	8.3; 8.4; 8.5	Added the definition of AESI and included AESIs in the reporting requirements to go along with SAEs
12/28/2020	Cover Page	Remove University Hospitals; Update Cleveland Clinic sub-investigators and study coordinator
12/28/2020	5.0	Registration contact information changed from Ben Pannell to the Study Coordinator provided on page 2
12/28/2020	8.5.1	SAE/AESI Reporting Requirements: study coordinator added to list of people included in notification
12/28/2020	6.1.3; 9.2	Adding biosimilar use of Rituximab is permitted for this study per treating investigator discretion
12/28/2020	10.3	Change Cleveland Clinic Biorepository shipping title and ATTN to Genevieve Crane, MD

Protocol Date	Section	Change
12/28/2020	6.5; 11.1.2; 11.2	Allowing virtual visits for long-term follow up visits
7/2/2021	Cover page	Updated study staff
7/2/2021	Abbrevia-tions	Removed unused abbreviations
7/2/2021	Table of contents	Added missing section numbers
7/2/2021	throughout	Corrected typos
7/2/2021	Schema; 11.1.1; 11.2	Added required PT/INR at screening to align with inclusion criteria
7/2/2021	9.1	Corrected storage temperature of acalabrutinib
7/2/2021	11.1.1	Removed requirement to receive approval for missing tissue samples prior to enrollment
7/2/2021	13.1	Replaced references to Forte EDC with the new name Adverra EDC

Figure 1: **STUDY SCHEMA**



PROTOCOL SUMMARY

Protocol Number/Title	CASE 3419/ Phase II Study of Rituximab and Acalabrutinib in Newly Diagnosed B Cell Post Transplant Lymphoproliferative Disorder (PTLD)
Study Phase	Phase II
Brief Background/Rationale	Post-transplant lymphoproliferative disorders (PTLD) are rare pathologically and clinically heterogeneous diseases that occur in both solid organ and bone marrow transplant (BMT) patients. The frequency of PTLD in solid organ transplant (SOT) varies from 1-20% with highest incidence seen among heart, lung, intestinal and multi organ transplantation [1-5] Currently there is no approved therapy for PTLD. Single agent rituximab is commonly used and the overall response rate (ORR) has ranged from 37% to 69% [6-11]. In a subset of patients' inadequate response necessitates addition of chemotherapy to improve response rate and outcomes. The morbidity and mortality with combination chemotherapy is reported to be high in this population [8]. In one analysis 52% patients treated with chemotherapy required hospital admission for complications and treatment related mortality was 26% [8]. Due to these reasons treatment with novel targeted agents needs to be explored to improve outcomes and to minimize toxicity. Acalabrutinib is a well-tolerated Bruton's Tyrosine Kinase Inhibitor (BTK). BTK plays an important role in B cell development and function thus its inhibition is a treatment strategy in B cell lymphomas. Acalabrutinib has been approved in the treatment of R/R mantle cell lymphoma (MCL) and is being studied in other B cell malignancies [12-15].
Primary Objective	To determine the overall response rate to combination treatment with rituximab and acalabrutinib in patients with PTLD. To be measured 8 weeks after treatment completion.
Secondary Objective(s)	To determine the following in patients with PTLD treated with combination rituximab and acalabrutinib. • Complete response rate (CRR) • Partial response rate (PRR) • Duration of response (DOR) • Progression free survival (PFS) • Overall survival (OS) • Time to treatment failure (TTF) • Safety of rituximab and acalabrutinib
Sample Size	62 patients
Disease sites/Conditions	Post-transplant lymphoproliferative disorder

Interventions	• Rituximab weekly x 4 weeks PLUS acalabrutinib 100mg BID x 4 weeks (28 day cycle) • Response assessment with CT scans on days 39-42 after end of cycle 1 treatment. • If complete response, then proceed with one additional 28 day cycle. • If partial response, then proceed with 3 additional 28 day cycles. • If stable disease or progression of disease, then go off study treatment and proceed onto LTFU.

ABBREVIATIONS

AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BCR	B cell receptor
BID	twice per day (dosing)
BOR	best overall response
BR	Bendamustine and Rituximab
BTK	Bruton tyrosine kinase
BMT	Bone marrow transplant
BUN	blood urea nitrogen
CBC	complete blood count
CCCC	Case Comprehensive Cancer Center
CCF	Cleveland Clinic Foundation
CFR	Code of Federal Regulations
CIs	confidence intervals
CLL	chronic lymphocytic leukemia
CR	complete response (remission)
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria For Adverse Events
CYP	cytochrome p450
DOR	duration of response
DSTC	Data Safety and Toxicity Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
IB	Investigator's brochure
IEC	independent ethics committee
Ig	immunoglobulin
IRB	institutional review board

IV	intravenous or intravenously
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MCL	mantle cell lymphoma
NE	nonevaluable
NHL	Non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PLL	prolymphocytic leukemia
PR	partial response (remission)
PRL	partial response with lymphocytosis
PRMC	Protocol Review and Monitoring Committee
PTLD	post-transplant lymphoproliferative disorders
R/R	relapsed/refractory
SAE	serious adverse event
SD	stable disease or standard deviation
SOC	Standard of Care
SOT	solid organ transplant
SUSAR	suspected unexpected serious adverse reaction
TTF	time to treatment failure
ULN	upper limit of normal

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1.0 Introduction

1.1 Background of PTLD

Post-transplant lymphoproliferative disorders (PTLD) are rare pathologically and clinically heterogeneous diseases that occur in both solid organ and bone marrow transplant (BMT) patients. The main determinant risk factors in the development of PTLD are the degree and duration of the immunosuppression. Suppression of the normal T cell function by the immunosuppressants enables the proliferation of EBV infected B cells leading to the development of PTLD.

The frequency of PTLD in solid organ transplant (SOT) varies from 1-20% with highest incidence seen among heart, lung, intestinal and multi organ transplantation [1-5]. The higher incidence of PTLD among these SOTs has been attributed to higher degree and longer duration of immunosuppression. The incidence is much less (1-5%) in SOT that requires lower immunosuppression like liver and renal transplants [4,5]. The incidence in BMT patients is low approximately 0.5-1% with T cell depletion being a risk factor [16-18].

The highest incidence of PLTD is in 1-2 years following the transplant. Early PTLD are mostly EBV positive, while the late PTLDs have shown to be EBV negative [19,20]. According to the 2016 WHO classification, PTLD is classified into 6 categories: plasmacytic hyperplasia PTLD, infectious mononucleosis PTLD, florid follicular hyperplasia PTLD, polymorphic PTLD, monomorphic PTLD and classical Hodgkin lymphoma PTLD [21]. Due to paucity of data and rarity of the disease there is no well-established standard of care for PTLD.

Currently, PTLD is treated with either single agent rituximab or with rituximab containing chemotherapy. The overall response rate (ORR) to single-agent rituximab has ranged from 37% to 69% [6-11]. The first prospective phase II study by Choquet et al evaluated single-agent rituximab in 43 SOT-related PTLD recipients who failed tapering of immunosuppression [7]. They demonstrated an ORR of 34%, event free survival (EFS) of 72%, and overall survival (OS) of 67% at 1 year. Complete response (CR) rate in this trial after 4 doses of rituximab was 28%. Rituximab was well tolerated with only 2 grade 3 or 4 events related to rituximab – hypertension and purpura with myalgia. Neutropenia was reported in two patients [7]. Another prospective study evaluated the efficacy of extended use of rituximab in 38 patients with PTLD [11]. After the first course of rituximab, 34% had a CR, which was further augmented to 61% when partial responders were given 4 additional doses. One episode of grade 4 neutropenia was the only serious adverse event observed. Elstrom et al retrospectively reviewed 35 patients with PTLD treated with rituximab and showed an ORR of 68% and median OS of 31 months with rituximab [8].

Currently there is no approved therapy for PTLD. Although single agent rituximab is commonly used to treat B cell PTLD, the overall response rate is around 60% with approximately 30% of the subjects attaining a complete response. In a subset of patients' inadequate response necessitates addition of chemotherapy to improve response rate and outcomes. The morbidity and mortality with combination chemotherapy is reported to be high in this population [8]. In one analysis 52% patients treated with chemotherapy required hospital admission for complications and treatment related mortality was 26% [8]. Due to these reasons treatment with novel targeted agents needs to be explored to improve outcomes and to minimize toxicity.

1.2 Name and Description of Acalabrutinib

1.2.1 Preclinical Data

Acalabrutinib is a potent inhibitor of BTK in vitro and in vivo. Pharmacology models have been used to define kinase selectivity of acalabrutinib in comparison to other BTK inhibitors, and to investigate functional effects of on-target and off-target activities. Acalabrutinib shows improved selectivity for BTK compared with ibrutinib [22]. Functional inhibition of non-target cells (eg, T cells, NK cells, platelets) was not observed for acalabrutinib at clinically relevant concentrations. Acalabrutinib is orally bioavailable in humans and is suitable for formulating in capsules. Acalabrutinib is approved in the US for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy. It is also being evaluated for the treatment of patients with other B-cell malignancies.

Please refer to the Investigator's Brochure (IB) for detailed preclinical data.

1.2.2 Clinical Efficacy Data

There have been several studies and are several ongoing studies that have evaluated the efficacy of acalabrutinib in B cell malignancies and even solid tumors. Acalabrutinib is approved for R/R mantle cell lymphoma and undergoing a phase III studies for use in chronic lymphocytic leukemia (CLL). A summary of results from studies evaluating acalabrutinib is below however, please see the Investigator Brochure for full details.

In a phase II study (ACE-LY-004) using single agent acalabrutinib to treat R/R MCL the ORR in 124 patients was 80.6% with 39.5% achieving a CR [23]. More than half of patients (56.6%) continued on treatment at a median follow up of 15 months. The median duration of response, PFS and OS were not reached, but the 1-year PFS and OS were 67% and 87% respectively [23] Most adverse events (AE) were grade 1-2, with only a small proportion of the patients experiencing grade ≥3 AE, which included neutropenia (10%), anemia (9%) and pneumonia (5%). Only 1 patient had grade 3 bleeding, while no atrial fibrillation was noted. Other notable AEs include grade 2 pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV) reactivation in 1 patient [23]. Acalabrutinib is being evaluated with Bendamustine and Rituximab (BR) for the treatment of MCL in a Phase 1b, multicenter, open label study (ACE-LY-106) [24] . The study includes two cohorts – treatment-naïve and R/R patients. The ORR was 94.4% (n=18) in the treatment-naïve cohort and 80.0% (n=20) in the R/R cohort. The phase III randomized placebo-controlled study evaluating BR vs BR + acalabrutinib in newly diagnosed MCL is currently accruing (clinicaltrials.gov #NCT02972840).

ACE-CL-001 is a phase I/II study of single agent acalabrutinib in 134 patients with R/R CLL, 99 patients with treatment-naïve CLL, 33 patients with CLL that were ibrutinib-intolerant, and 29 patients with Richter's syndrome or prolymphocytic leukemia transformation (PLL) [25]. Acalabrutinib 100 mg twice-daily dose demonstrated 99% BTK occupancy. In the R/R CLL cohort, ORR (including PR and PRL) was 96.9% with most responses being PR (86.8%) at a median follow up of 19.8 months. The rate of PFS at 12 months was 95.4% [13,14]. In the treatment-naïve and ibrutinib intolerant cohorts the ORRs were 99% and 80.6%, respectively. In the Richter's syndrome or PLL group the ORR was 37%. Ongoing studies are evaluating acalabrutinib in combination with chemotherapy in various subtypes of B cell malignancies.

1.2.3 Clinical Pharmacokinetics

Acalabrutinib is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center and acalabrutinib is the S-enantiomer. See the IB for further details regarding pharmacokinetics. In brief, Acalabrutinib is absorbed rapidly in non-clinical

species. It is almost completely metabolized by multiple CYP and non CYP metabolic pathways with CYP3A-mediated oxidation being the major route of metabolism. The half-life of the active metabolite (ACP-5862) is 6.9 hours. Acalabrutinib is excreted mostly in the feces (84%) and a small amount in the urine (12%).

1.3 Name and Description of Rituximab

Rituximab has been approved for the use in Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), Rheumatoid Arthritis, Granulomatosis with Polyangiitis and Microscopic Polyangiitis, and Pemphigus Vulgarius [26]. While not approved for PTLD, it has become the mainstay of treatment (see Section 1.1 for further details)

1.3.1 Preclinical Data

Rituximab is a genetically engineered, chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant pre-B and mature B cells. The antibody is an IgG1 κ immunoglobulin containing murine light-and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular mass of 145 kD. The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes with a binding affinity of ~8.0nM. The Fc domain recruits immune effector functions. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow [26].

1.3.2 Clinical Efficacy Data

See section 1.1 for discussion of rituximab use in patients with PTLD.

1.3.3 Clinical Pharmacokinetics

Per the rituximab package insert, pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m2 rituximab weekly by intravenous infusion for 4 doses. Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment. The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone. Based on a population pharmacokinetic analysis of data from 298 NHL patients who received rituximab once weekly or once every three weeks, the estimated median terminal elimination half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the pharmacokinetics of rituximab.
Pharmacokinetics were characterized in 21 patients with CLL receiving rituximab according to the recommended dose and schedule. The estimated median terminal half-life of rituximab was 32 days (range, 14 to 62 days) [26].

1.4 Rationale

As stated in the Section 1.1, there is currently no approved therapy for PTLD. Single agent rituximab and combination chemotherapy (R-CHOP) are the treatments used in clinical practice. Single agent rituximab yields a response rate of around 60% and combination chemotherapy is associated with significant morbidity and mortality[8]. As there are no approved treatment for newly diagnosed or relapsed PTLD, it's an area of unmet need. Due to these

reasons treatment with novel targeted agents needs to be explored to improve outcomes and to minimize toxicity.

Bruton's tyrosine kinase (BTK) is a non-receptor enzyme in the Tec kinase that plays an important role in B-cell development and function. It is in the B-cell receptor (BCR) signaling pathway and leads to the activation of nuclear factor kB and thus cell migration, proliferation and survival. Abnormal signaling of the BCR pathway is important in the pathogenesis of B-cell malignancies. Thus, inhibition of the BTK has been implicated in the treatment of B-cell malignancies [12,15]

Acalabrutinib is a highly selective, irreversible second-generation Bruton's tyrosine kinase (BTK) inhibitor that is approved for the treatment of mantle cell lymphoma (MCL), a B cell malignancy. It is also active in CLL and studies are ongoing evaluating its efficacy in other B cell lymphomas. This drug is rapidly absorbed and eliminated reaching the mean peak plasma level between 0.6 to 1.1 hours with a mean half-life of 1 hour in CLL patients [13]. This short half-life compared to 4-6 hours for ibrutinib [27] could be partially responsible for its better safety profile. Unlike ibrutinib, published data suggests lack of inhibition of epidermal growth factor receptor (EGFR), interleukin-2 inducible T cell kinase (ITK) and tyrosine kinase expressed in hepatocellular carcinoma (TEC) by acalabrutinb [13]. An aggregate safety analysis of acalabrutinib monotherapy was conducted and included data from 7 studies. This pooled data included 614 acalabrutinib-exposed subjects with a median exposure of 21.9 months. The most frequently reported Grade ≥3 AEs were neutropenia (10.4%), anemia (7.5%), pneumonia (6.5%), thrombocytopenia (3.7%), and hypertension (3.1%). Evidence of clinical activity with improved toxicity profile has led to clinical studies with this agent in B cell malignancies.

Ongoing studies are evaluating combination of acalabrutinb in various subtypes of B cell malignancies. Some of which include acalabrutinb with bendamustine and rituximab (BR) in RR MCL (NCT02717624), and in combination with R-CHOP in DLBCL (ACCEPT trial). An ongoing trial in United Kingdom is evaluating the outcome of ibrutinib with R-CHOP in PTLD patients (https://bloodwise.org.uk/research/clinical-trials/ptld-ibrutinib-i-and-rituximab-r-and-ir-chop). Based on emerging data of clinical efficacy of acalabrutinib in B cell malignancies and an unmet need for novel therapies in PTLD, we propose a phase II study of rituximab and acalabrutinib in newly diagnosed B cell PTLD.

2.0 Objectives

2.1 Primary Objective

To determine the overall response rate to combination treatment with rituximab and acalabrutinib in patients with newly diagnosed B-cell PTLD.

2.2 Secondary Objectives

To determine the following in patients with PTLD treated with combination rituximab and acalabrutinib.

- Complete response rate (CRR)
- Partial response rate (PRR)
- Duration of response (DOR)
- Progression free survival (PFS)
- Overall survival (OS)
- Time to treatment failure (TTF)
- Safety of rituximab and acalabrutinib

3.0 Study Design

3.1 Study design

This is a non-randomized phase II study of acalabrutinib plus rituximab in newly diagnosed B-cell PTLD in both SOT and BMT patients. All subjects who meet the eligibility criteria described below will be enrolled to participate in the study.

Refer to Section 11 for a comprehensive list of study assessments and their timing. The study schema is provided in Figure 1 at the beginning of this document

3.2 Number of Subjects

We plan to enroll 62 patients.

3.3 Replacement of Subjects

If a subjects signs consent and meets eligibility criteria, but withdraws from the study prior to receiving the study treatment, the subject will be replaced. No subject will be replaced after receiving study treatment.

3.4 Expected Duration of Treatment and Subject Participation

Duration of treatment will depend on patients' response to therapy. Initial treatment (cycle 1) for all patients, will be 28 days in length. Between days 39-42 after the end of cycle 1 treatment, patients will undergo CT scan for response assessment. Patients with a complete response will receive one additional 28 day cycle of therapy. Patients with a partial response will receive 3 additional 28 day cycles of therapy. Patients with stable disease or progressive disease will come off study treatment and go directly on to long-term follow-up. Patients will receive a minimum of 1 cycle of therapy and a max of 4 cycles depending on their response. Cycle 2 should start within 2 weeks after the end of cycle 1 treatment.

Table 1: Total Duration of Treatment Based on Disease Response

Response to Cycle 1	Duration of Treatment
Complete Response	56 days
Partial Response	112 days
Stable or Progressive Disease	28 days

4.0 Subject Selection

Each of the criteria in the sections that follow must be met in order for a subject to be considered eligible for this study. Use the eligibility criteria to confirm a subject's eligibility.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment:

4.1.1 Subjects must have a biopsy confirmed newly diagnosed CD20 positive B cell PTLD. The histological diagnosis may include:

- Plasmacytic hyperplasia PTLD
- Infectious mononucleosis PTLD
- Florid follicular hyperplasia PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B- cell types)
- Classical Hodgkin lymphoma PTLD

4.1.2 Patients ≥ 18 years of age.

4.1.3 Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. ECOG 3 will be permitted if the decline in performance status is due to lymphoma. [See Appendix 1]

4.1.4 Subjects must have adequate hematologic, hepatic, and renal function as defined below:

- Hemoglobin ≥ 8 gm/dL
- Absolute neutrophil count ≥1000/mcL (unless documented bone marrow involvement with lymphoma)
- Platelet count ≥50000/mcL (unless there is documented bone marrow involvement with lymphoma)
- Prothrombin time/INR or aPTT (in the absence of Lupus anticoagulant) < 2x ULN.
- Total bilirubin ≤1.5X upper limit of normal (ULN)
- Creatinine ≤2.5X upper limit of normal (ULN) or creatinine clearance ≥40 ml/min using the Cockcroft-Gault equation (Appendix 4)
- ALT/AST < 2.5 X or ≤5X ULN for patients with documented hepatic involvement with lymphoma

4.1.5 Women of childbearing potential and men must agree to use highly effective methods of contraception during treatment and for 12 months after last dose of study treatment. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomy of a female subject's male partner (with medical assessment and confirmation of vasectomy surgical success
- Sexual abstinence (only if refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)

Women who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential.

4.1.6 Subjects must be willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty

4.1.7 Subjects must have the ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information

4.2 Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment:

4.2.1 Prior treatment with any BTK inhibitor

4.2.2 Subjects receiving any other investigational agents or participating in another therapeutic clinical trial.

4.2.3 Subjects with active (treated or untreated) brain metastases/ central nervous system (CNS) disease (including but not limited to CNS PTLD) will be excluded from this clinical trial

4.2.4 Prior malignancy (or any other malignancy that requires active treatment), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, early stage prostate cancer or other cancer from which the subject has been disease free for ≥ 3 years

4.2.5 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. Subjects with controlled, asymptomatic atrial fibrillation during screening can enroll in the study.

4.2.6 Has difficulty with or is unable to swallow oral medication, or has significant gastrointestinal disease that would limit absorption of oral medication.

4.2.7 Known history of infection with HIV. HIV-positive subjects on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with acalabrutinib.

4.2.8 Patients with uncontrolled concurrent illness like active infection (eg, bacterial, viral, or fungal) requiring IV antibiotics or psychiatric illness/social situations that would limit compliance with study requirements

4.2.9 Known history of drug-specific hypersensitivity or anaphylaxis to acalabrutinib or rituximab (including active product or excipient components).

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

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

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

4.2.13 Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon)

4.2.14 Requires treatment with proton pump inhibitors (eg, 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.

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

4.2.16 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.

4.2.17 Hepatitis B or C serologic status: subjects who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR). Those who are hepatitis B surface antigen (HbsAg) positive or hepatitis B PCR positive will be excluded. Subjects who are hepatitis C antibody positive will need to have a negative PCR result. Those who are hepatitis C PCR positive will be excluded.

4.2.18 History of progressive multifocal leukoencephalopathy (PML)

4.2.19 Breastfeeding or pregnant. Pregnant or breastfeeding women are excluded from this study because it is unknown how acalabrutinib and rituximab can affect the fetus or infant. Rituximab can cross the placenta and is found in breast milk. Acalabrutinib

has been found in the breast milk of animals and there is not significant data regarding its effect during pregnancy.

4.2.20 Vaccination with live virus vaccines is not allowed within 4 weeks of study treatment of or during treatment.

4.2.21 Active GVHD requiring treatment

4.2.22 Patients with biopsy proven transplant organ rejection that is clinically significant as determined by transplant team

4.3 Inclusion of Women and Minorities

Men, women and members of all races and ethnic groups are eligible for this trial.

5.0 Registration

All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through Cleveland Clinic and will be provided a study number by emailing the Study Coordinator with the contact information provided on page 2 of this document.

6.0 Treatment Plan

6.1

Table 2: Treatment Regimen Overview

Cycle	Agent	Suggested Premedication[3]	Dose	Route	Schedule	Cycle Length
Cycle 1	Rituximab	Acetaminophen (650 mg) PO and diphenhydramine (50 mg) PO or IV, 30 -60 minutes prior to each infusion[1].	375mg/m^2 IV **or** flat dose 1400mg SC	IV **or** subcutaneous (SC)	Days 1,8,15,22	28 days
Cycle 2 for subjects in CR	Rituximab	Acetaminophen (650 mg) PO and diphenhydramine (50 mg) PO or IV, 30 -60 minutes prior to each infusion[1].	375mg/m^2 IV **or** flat dose 1400mg SC	IV **or** subcutaneous (SC)	Days 1,8,15,22	
Cycles 2-4 for subjects in PR	Rituximab	Acetaminophen (650 mg) PO and diphenhydramine (50 mg) PO or IV, 30 -60 minutes prior to each infusion[1].	375mg/m^2 IV **or** flat dose 1400mg SC	IV **or** subcutaneous (SC)	Day 1	
Cycles 1-4	Acalabrutinib	none	100mg BID	PO	Days 1-28	

1. Hydroxyzine may be substituted in patients intolerant of diphenhydramine
2. First dose of rituximab will be given IV and subsequent doses can be either IV or SC based on institutional guidelines.
3. Premedication can be per institutional standards or as suggested above

If a patient is on immunosuppressants, the treating physician will discuss with the transplant team about reducing immunosuppression according to local institutional standard of care. If the transplant team decides to reduce the immunosuppression, the study treatment can be started simultaneously and it is not required to fail the trial of immunosuppression to start the study treatment. If the transplant team deems that it is not safe to reduce the immunosuppression, eligible patients can start study treatment.

6.1.1 Criteria for starting a new cycle

The following treatment parameters should be met on D1 prior to initiating a new cycle (starting with cycle 2):

- ANC ≥500/mcL
- Platelets ≥50,000/mcL (if there is documented bone marrow involvement or hypersplenism, then platelets ≥ 25,000/mcL)
- Any non-hematologic grade 3 or 4 AE that is considered at least possibly related to study treatment that has resolved to Grade ≤1.

Growth factors can be used as per institutional standard to treat/prevent neutropenia. The use of growth factors should be documented in the CRF.

6.1.2 Acalabrutinib Administration

Patients will receive acalabrutinib 100mg BID orally on days 1-28. See Table 2 above for further details. Also refer to the drug diary (appendix IV) for further directions. On days with rituximab administration, acalabrutinib may be taken first in order to allow 12 hours between dosing.

The capsules should be swallowed intact with water. Subjects should not attempt to open capsules or dissolve them in water. Acalabrutinib can be taken with or without food.
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.

Drug interactions for Acalabrutinib are described in Section 6.3.

Appropriate dose modifications for Acalabrutinib are described in Section 7.0.

Reported adverse events and potential risks of Acalabrutinib are described in Section 8.0.

6.1.3 Rituximab Administration

Patients will receive Rituximab on days 1, 8, 15, and 22 of 28 day cycles during cycle 1 and day 1 (for PR responders) or days 1, 8, 15, and 22 (for CR responders) of subsequent cycles (see Table 2 above). First dose will be administered IV per institutional standard and subsequent doses can be given either IV or SQ per institutional guidelines. CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. See Table 2 above for further details.

Rituximab biosimilar use is permitted for this study per treating investigator discretion or per insurance mandate.

Appropriate dose modifications for Rituximab are described in Section 7.0. Reported adverse events and potential risks of Rituximab are described in Section 8.0.

6.2 Duration of Therapy

See Section 3.4

6.3 General Concomitant Medications and Supportive Care Guidelines

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc when appropriate.

Patients with hepatitis B core antibody positive and HBV viral DNA PCR negative should receive prophylaxis with either lamuvidine or entecavir (per institutional standard) while receiving rituximab and for 6 months after last dose of rituximab

Any chemotherapy, anticancer immunotherapy (other than Rituximab), corticosteroids (at dosages equivalent to prednisone > 20 mg/day for longer than 2 weeks), experimental therapy (other than acalabrutinib), or radiotherapy for treating PTLD are prohibited.

Warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) are prohibited.

The concomitant use of strong inhibitors/inducers of CYP3A4 (see Appendix 2) should be avoided when possible. If a subject requires a strong CYP3A inhibitor while on study, monitor the subject closely for potential toxicities.

Subjects should avoid the use of calcium carbonate-containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. H2-receoptor antagonists should be avoided or taken hours after taking acalabrutinib. H2-receptor antagonists should be taken approximately 2 hours after an acalabrutinib dose. 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. However, the decision to treat with proton-pump inhibitors during the study is at the investigator's discretion, with risks and benefits reviewed.

6.3.1 Drug-Drug Interactions with Acalabrutinib

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated.

However, acalabrutinib is metabolized by CYP3A. Concomitant administration of acalabrutinib with a strong CYP3A and P-glycoprotein (P-gp) inhibitor, itraconazole increased exposure by approximately 5-fold. Conversely, concomitant administration of acalabrutinib with a strong CYP3A inducer, rifampin decrease acalabrutinib exposure and could reduce efficacy. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 2) 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, the subject should be monitored closely for any potential toxicities.

The effect of agents that reduce gastric acidity (eg, proton pump inhibitors or antacids) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). 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 at least 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. However, the decision to treat with proton-pump inhibitors during the study is at the investigator's discretion, with an understanding of the potential benefit to the subject's gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib.

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.

6.3.2 Drug-Drug Interactions with Rituximab

No known drug-drug interactions. However, limited data are available on the safety of the use of biologic agents or disease modifying antirheumatic drugs (DMARDs) other than methotrexate in RA patients exhibiting peripheral B-cell depletion following treatment with rituximab. Observe patients closely for signs of infection if biologic agents and/or DMARDs are used concomitantly

6.4 Criteria for Removal from Study

Treatment may continue for 2-4 cycles or until one of the following criteria applies:

- Disease progression
- Development of second primary malignancy
- Intercurrent illness that prevents further administration of treatment
- The investigator considers it, for safety reasons, to be in the best interest of the subject
- Unacceptable adverse event(s) (Any toxicity or other issue that causes a delay of study drug administration by more than 4 weeks)
- Subject decision to withdraw from treatment (partial consent) or from the study (full consent),
- Pregnancy during the course of the study for a child-bearing participant
- Death
- Sponsor reserves the right to temporarily suspend or prematurely discontinue this study.

The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

6.5 Duration of Follow Up

End of Treatment Response Assessment: End of treatment scans and visit will be completed within 8 weeks (±7 days) of treatment termination. Subjects with stable or progressive disease after Cycle 1 Day 36 scans will go directly onto LTFU.

If there is an adverse event related to study drug, the clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause with a cut off of 24 months after completion of therapy.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

Long-Term Follow Up

Each subject should be followed for a total of 3 years after study treatment has ended, Follow up visits will occur at 6, 12, 18, 24 and 36 months after completion of treatment. During this period, subjects will be followed via physical exam and laboratory analysis. CT scans will be repeated at 6, 12, and 24 months. If the patient is unable to follow up in person, virtual visits may be used to capture applicable procedures during long-term follow up only. Subjects who

experience disease progression are not required to come in for clinic follow up. Study team will make every effort to contact them via phone to obtain information specified in the protocol (see section 11.1.2).

7.0 Dose Delays/Dose Modifications

7.1 Acalabrutinib

Subjects should be followed closely for AEs or laboratory abnormalities that might indicate acalabrutinib-related toxicity. If a subject experiences an acalabrutinib-related toxicity or other intolerable AE during the course of therapy, then acalabrutinib should be withheld, as necessary, until the AE resolves or stabilizes to an acceptable degree.

Dose modifications for the following acalabrutinib-emergent toxicities are provided in Table 3:

- Grade 4 neutropenia (< 500/μL) for > 7 days
- Grade 3 thrombocytopenia in presence of significant bleeding.
- Grade 4 thrombocytopenia.
- 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.

Table 3: Drug Modification Actions for Acalabrutinib

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 lower dose 100 mg daily
3rd	For non-hematologic AE's, discontinue acalabrutinib. For thrombocytopenia with significant bleeding, discontinue acalabrutinib. For other hematologic AEs, hold acalabrutinib until recovery to Grade 1 or baseline; restart at lower dose 100 mg daily .
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. As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (eg, once per week) until abnormalities have recovered to Grade 1. 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 acalabrutinib-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 and after discussion with the sponsor-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. The maximum dose of acalabrutinib is 100 mg BID.

Treatment with acalabrutinib should be withheld for any unmanageable, potentially acalabrutinib-related toxicity that is Grade ≥ 3 in severity. Any other clinically important events where dose delays may be considered appropriate must be discussed with the Sponsor-Investigator, Dr. Deepa Jagadeesh.

Consider the benefit-risk of withholding acalabrutinib for 3-7 days pre- and post-surgery depending on the surgery and the risk of bleeding.

7.2 Rituximab

Because rituximab is known to cause hypersensitivity and infusion reactions, it will be infused with graduated incremental rates depending on whether it is being given as an initial dose (cycle 1) or subsequent dose (2-4), per institutional guidelines. As the severity of infusion reactions increase, the infusion of rituximab will be either slowed or held, as indicated in table 4.

Table 4: Management of Rituximab Hypersensitivity/Infusion Reactions

Grade of Event	Management/Next Dose for Rituximab	Treatment
Grade 1	Decrease infusion rate by one dose level (see section 9.2 for rate information)	Treatment of infusion-related symptoms with diphenhydramine and acetaminophen is recommended. Additional treatment with bronchodilators or IV saline may be indicated.
Grade 2	Hold until ≤ Grade 1. The infusion can be resumed at one-half the previous rate when symptoms abate.	
Grade 3	Hold until ≤ Grade 1. The infusion can be resumed at one-half the previous rate when symptoms abate.	
Grade 4	Off protocol therapy.	Epinephrine for subcutaneous injection, diphenhydramine hydrochloride for IV injection, corticosteroids as needed and resuscitation equipment for the emergency management of anaphylactic reactions will be available at the bedside prior to rituximab administration.

8.0 Adverse Events and Potential Risks

8.1 Acalabrutinib

See Section 5.3.2 of the Investigator Brochure for further information. A summary is provided here. An aggregate safety analysis of acalabrutinib monotherapy was conducted and included data from 7 studies. This pooled data included 614 acalabrutinib-exposed subjects with a median exposure of 21.9 months. Almost all subjects (609 [99.2%]) had at least 1 AE, and about half (334 [54.4%]) had at least 1 Grade ≥3 AE. The most commonly reported AEs of any grade were headache (42.3%), diarrhea (40.4%), fatigue (24.6%), nausea (23.6%), contusion (23.5%), cough (22.1%), and upper respiratory tract infection (21.7). Atrial fibrillation of any grade was seen in

22 (3.6%) patient, grade 3 events were seen in 8 (1.3%) patients, and grade 4 or 5 events were seen in 0 patients. The most frequently reported Grade ≥3 AEs were neutropenia (10.4%), anemia (7.5%), pneumonia (6.5%), thrombocytopenia (3.7%), and hypertension (3.1%). Grade 5 AEs were reported for 27 (4.4%) patients with the most common severe AE being infection (2.1%).

8.1.1 Warnings and Precautions

8.1.1.1 Hemorrhage

Serious hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported in clinical trials with acalabrutinib; some of these bleeding events resulted in fatal outcomes. Grade 3 or higher bleeding events, including gastrointestinal, intracranial, and epistaxis have been reported in 2% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in approximately 50% of patients with hematological malignancies. The mechanism for hemorrhage is not well understood. Acalabrutinib may further increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for 3-7 days pre- and post-surgery depending on the surgery and the risk of bleeding.

8.1.1.2 Infection

Serious infections (bacterial, viral or fungal), including fatal events and opportunistic infections, have been reported in clinical studies with acalabrutinib. The most frequently reported Grade 3 or 4 infection was pneumonia. Across the acalabrutinib clinical development program (including subjects treated with acalabrutinib in combination with other drugs), cases of hepatitis B virus (HBV) reactivation (resulting in liver failure and death in 1 case) and cases of progressive multifocal leukoencephalopathy have occurred in subjects with hematologic malignancies. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

8.1.1.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Subjects should be closely monitored as appropriate.

8.1.1.4 Second Primary Malignancies

Second primary malignancies, including solid tumors and skin cancers, have been reported in patients treated with acalabrutinib. The most frequent second primary malignancy was skin cancer (basal cell carcinoma). Subjects should be monitored for signs and symptoms of malignancy. Subjects who develop a second primary malignancy should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated, and it may be necessary for subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the principal investigator.

8.1.1.5 Atrial Fibrillation

Events of atrial fibrillation/flutter have been reported in clinical studies with acalabrutinib, particularly in subjects with cardiac risk factors, hypertension, diabetes mellitus, acute infections, and a previous history of atrial fibrillation.
The mechanism for atrial fibrillation is not well understood

8.2 Rituximab

See Section 6 of the package insert for a detailed discussion of adverse events. In NHL the most common (≥25%) adverse reactions in clinical trials were infusions reactions, fever, lymphopenia, chills, infection, and asthenia [26]. In CLL the most common (≥25%) adverse reactions in clinical trials were infusions reactions and neutropenia [26].

8.2.1 Warnings and Precautions

8.2.1.1 Tumor Lysis Syndrome

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, sometimes fatal, can occur within 12-24 hours after the first infusion of rituximab in patients with NHL. A high number of circulating malignant cells (≥25,000/mm3) or high tumor burden, confers a greater risk of TLS [26]. Correct electrolyte abnormalities; monitor renal function and hydration status, and administer supportive care as indicated.

8.2.1.2 Infection

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of rituximab-based therapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia >11 months after rituximab exposure). New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue rituximab for serious infections and institute appropriate anti-infective therapy. Rituximab is not recommended for use in patients with severe, active infections [26].

8.2.1.3 Cardiovascular Adverse Reactions

Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock may occur in patients receiving RITUXAN. Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of RITUXAN for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina [26].

8.2.1.4 Renal Toxicity

Severe, including fatal, renal toxicity can occur after rituximab administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. Monitor closely for signs of renal failure and discontinue rituximab in patients with a rising serum creatinine or oliguria [26].

8.2.1.5 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy. In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1-77) days in patients with NHL. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur [26].

8.2.1.6 Immunization

The safety of immunization with live viral vaccines following rituximab therapy has not been studied and vaccination with live virus vaccines is not recommended before or during treatment [26].

8.2.1.7 Embryo-Fetal Toxicity

Based on human data, rituximab can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in-utero. Advise pregnant women of the risk to a fetus. Females of

childbearing potential should use effective contraception while receiving rituximab and for 12 months following the last dose of rituximab [26].

8.2.1.8 Concomitant Use with Other Biologic Agents and DMARDS other than Methotrexate in RA, GPA and MPA, PV

Limited data are available on the safety of the use of biologic agents or disease modifying antirheumatic drugs (DMARDs) other than methotrexate in RA patients exhibiting peripheral B-cell depletion following treatment with rituximab. Observe patients closely for signs of infection if biologic agents and/or DMARDs are used concomitantly. Use of concomitant immunosuppressants other than corticosteroids has not been studied in GPA or MPA or PV patients exhibiting peripheral B-cell depletion following treatment with rituximab [26].

8.2.1.9 Infusion-Related Reactions

[US Boxed Warning]: Serious (including fatal) infusion-related reactions have been reported, usually with the first infusion; fatalities have been reported within 24 hours of infusion; monitor closely during infusion; discontinue for severe reactions and provide medical intervention for grades 3 or 4 infusion-related reactions. Reactions usually occur within 30 to 120 minutes and may include hypotension, angioedema, bronchospasm, hypoxia, urticaria, and, in more severe cases, pulmonary infiltrates, acute respiratory distress syndrome, MI, ventricular fibrillation, cardiogenic shock, and/or anaphylactoid events. Closely monitor patients with a history of prior cardiopulmonary reactions or with preexisting cardiac or pulmonary conditions and patients with high numbers of circulating malignant cells ($\geq$25,000/mm^3). Prior to infusion, premedicate patients with acetaminophen and an antihistamine (and methylprednisolone for patients with rheumatoid arthritis [RA] and PV). Medications for the treatment of hypersensitivity reactions (eg, bronchodilators, epinephrine, corticosteroids, oxygen) should be available for immediate use; treatment is symptomatic. If infusion-related reaction occurs, temporarily or permanently discontinue infusion (depending on the severity of the reaction and required interventions). After symptoms resolve, infusion may be resumed with at least a 50% infusion rate reduction [26].

8.2.1.10 Mucocutaneous Reactions

[US Boxed Warning]: Severe and sometimes fatal mucocutaneous reactions (lichenoid dermatitis, paraneoplastic pemphigus, Stevens-Johnson syndrome, toxic epidermal necrolysis, and vesiculobullous dermatitis) have been reported; onset has been variable but has occurred as early as the first day of exposure. Discontinue in patients experiencing severe mucocutaneous skin reactions [26].

8.2.1.11 Progressive multifocal leukoencephalopathy

[US Boxed Warning]: Progressive multifocal leukoencephalopathy (PML) due to JC virus infection has been reported with rituximab; may be fatal. Clinical findings included confusion/disorientation, motor weakness/hemiparesis, altered vision/speech, and poor motor coordination with symptoms progressing over weeks to months. Promptly evaluate any patient presenting with neurological changes; consider neurology consultation, brain MRI, and lumbar puncture for suspected PML. Discontinue rituximab in patients who develop PML; consider reduction/discontinuation of concurrent chemotherapy or immunosuppressants [26].

8.3 Definitions

8.3.1 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result

of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

The following are NOT considered an AE:

- **Pre-existing condition that has not worsened**: A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Preplanned hospitalization**: A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the preplanned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before signing the ICF, will not be considered serious if they are performed after signing the ICF for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic testing and procedures**: Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported. If a test or procedure is done to rule out a diagnosis, the sign or symptom leading to the test/procedure should be the event term, and the event term should only be updated to the diagnosis if/when the diagnosis is confirmed. Testing and procedures performed solely as screening measures (eg, routine screening mammography or colonoscopy) should not be reported as AEs or SAEs.
- **Abnormal laboratory results that the investigator considers to not be clinically significant**: Abnormal laboratory results are not AEs unless they are clinically significant. For example, a clinically significant laboratory result is one that requires treatment (for example a blood transfusion for low hemoglobin) or requires a change in study drug (eg, lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).
- **Progression of underlying malignancy**: Progression of underlying malignancy will not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the underlying malignancy, or if they do not fit the expected pattern of progression for the disease under study.
  If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

Symptomatic deterioration may occur in some subjects. Symptomatic deterioration is when progression is evident in the subject's clinical symptoms and the investigator may elect not to perform further disease assessments. If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

8.3.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

8.3.3 Adverse Events of Special Interest

The following events are adverse events of special interest (AESIs) and must be reported to the sponsors expeditiously, irrespective of regulatory seriousness criteria or causality:

- Ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.)

8.3.4 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur on or after cycle 1 day 1 are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE v5.0)
- Description of the event
- Date of onset and resolution
- Expectedness of the toxicity
- Grade of toxicity (as per CTCAE)
- Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version **5** will be utilized for AE reporting. If the event term is not listed in CTCAE v5.0, then the general grading scale shown here will be used.

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol. For regulatory reporting purposes, only events listed in the Investigator Brochure's Reference Safety Information will be considered expected.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

Protocol must specify if attribution is required for individual components of the treatment regimen or the treatment regimen as a whole.

8.4 SAE/AESI Report Form

SAEs/AESIs will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

8.5 Reporting Procedures for Serious Adverse Events and AESIs

For the purposes of safety reporting, all adverse events will be reported that occur on or after Cycle 1 Day 1 through the End of Treatment Response Assessment. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs/AESIs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

8.5.1 SAE/AESI Reporting Requirements

- Participating investigators (all sites) must report all serious adverse events and AESIs to the Lead Site Principal Investigator (e.g. Sponsor-Investigator) within **1 business day** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE/AESI until final resolution.
    - Please send all SAE/AESI reports to cancersaeinbox@ccf.org and cc: jagaded@ccf.org and the study coordinator listed on page 2.
- The Lead Site Principal Investigator will review the SAE and report the event to the FDA, external collaborator(s), and Cleveland Clinic IRB as applicable.
- It is the Sponsor-Investigator's responsibility (e.g. lead site PI) to ensure that ALL serious adverse events that occur on the study (e.g. ALL SAEs that occur at each enrolling institution) are reported to all participating sites.

Drug Supplier / Manufacturer / Financial Supporter Reporting Requirements:

- The investigator is responsible for ensuring that all AEs and SAEs/AESIs that are observed or reported during the study, as outlined in the prior sections, are recorded on the CRF
- It is the responsibility of the Sponsor-Investigator (Cleveland Clinic Principal Investigator) to report safety data to the drug supplier (AstraZeneca Data Entry Site [DES]).
- The Sponsor will submit appropriate reports to applicable local regulatory agencies and to ethics committees (ECs) as per local regulations. The Sponsor will notify Acerta Pharma/AstraZeneca in parallel with submission to the IRB (if applicable) and concerned Regulatory Authority for Suspected Unexpected Serious Adverse Reactions (SUSARs) and within fifteen (15) calendar days of awareness for other SAEs or Special Situation Reports using Form FDA 3500A (MedWatch). New information will be submitted to Acerta Pharma/AstraZeneca within the same time frame as initial reports.
- Whenever possible, SAEs should be reported by diagnosis term not as a constellation of symptoms.
- Death due to disease progression should be recorded on the appropriate form in the electronic data capture (EDC) system. If the primary cause of death is disease progression, the death due to disease progression should not be reported as an SAE to Acerta Pharma/AstraZeneca. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause

of death as the event 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. Autopsy and postmortem reports will be forwarded if readily available to Acerta Pharma/AstraZeneca DES as outlined above.

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

All SAEs/AESIs will be submitted by the lead site to the AstraZeneca Product Safety mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com

Institutional Review Board Reporting Requirements:

- Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

Pregnancy

Investigators should report all pregnancies and pregnancies in the partners of subjects to the Sponsor within 24 hours. The Sponsor should report any occurrences to the Cleveland Clinic IRB and Regulatory Authorities per institutional and/or regulatory guidelines, and to Acerta Pharma/AstraZeneca per contractual guidelines. Each participating site should follow their local institutional IRB reporting policies.

Any uncomplicated pregnancy that occurs with the subject or with the partner of a treated subject during this study will be reported. All pregnancies and partner pregnancies that are identified during or after the last dose of study medication will be reported, followed to conclusion, and the outcome reported.

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving study drug who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Overdose

Clinical information relevant to overdose is not available. For results from nonclinical overdose studies in rats and dogs, please refer to the Investigator Brochure.

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the appropriate CRF and the sponsor-investigator should be notified immediately.

8.6 SAEs and OnCore

- All SAEs will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into Oncore.

8.7 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.8 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Sections 8.1 and 8.2.

9.1 Acalabrutinib

Other Names: ACP-196

Product description: Acalabrutinib capsules for oral administration, are supplied as yellow and blue, opaque hard gelatin capsules, 100 mg strength (size 1), and with acalabrutinib as an 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).

Storage requirements: Acalabrutinib capsules are packaged in white, high-density polyethylene bottles and should be stored according to the storage conditions as indicated on the label. The recommended storage condition for acalabrutinib capsules is below 86°F.

Route of administration: Oral administration

Drug Procurement: Acalabrutinib will be supplied for this study by Acerta Pharma.

Drug Accountability: The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

Drug Destruction: At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

9.2 Rituximab

Other Names: Rituxan™, Mabthera™

Product description: Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. The product is formulated for intravenous administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5. Rituximab biosimilar use is permitted for this study per treating investigator discretion or per insurance mandate.

Solution preparation: Using appropriate aseptic technique, withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride or 5% Dextrose in Water. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody. Do not mix or dilute with other drugs.

Storage requirements: Once reconstituted into IV bags, rituximab is chemically stable for up to 24 hours at 2°C to 8°C (36°F to 46°F), followed by up to 24 hours at room temperature (23°C). However, since rituximab solutions do not contain preservative, diluted solutions should be stored refrigerated (2°C to 8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed. Rituximab vials should be protected from direct sunlight.

Stability: Rituximab is biologically and chemically stable at 2°C to 8°C (36°F to 46°F) and has a proposed shelf life stability of 30 months. Rituximab vials are intended for single use only. Do not use beyond the expiration date stamped on the carton.

Route of administration:
DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Do not infuse rituximab concurrently with another IV solution or other IV medications. Premedication, consisting of acetaminophen 650 mg to 1000 mg PO and diphenhydramine 25 to 50 mg IV or PO, will be administered before each infusion of rituximab. Premedication may attenuate infusion-related events. Since transient hypotension may occur during rituximab infusion, anti-hypertensive medications will be withheld 12 hours prior to rituximab infusion.

Rituximab will be administered intravenously per institutional standard. An in-line filter is not required.

Rituximab infusion must be interrupted for severe reactions. If the patient experiences fever and rigors, the antibody infusion is discontinued. The severity of the side effects will be evaluated. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms have completely resolved. Most patients who have experienced non-life-threatening infusion-related reactions have been able to complete the full course of rituximab therapy.

NOTE: In addition, alternative rituximab infusion rates (i.e., “rapid rituximab infusion”) can be used per institutional guidelines as long as the total number of milligrams of rituximab is the

same and that "rapid infusion" is not administered with the patient's first rituximab cycle. Further, a rituximab infusion time should not be less than 90 minutes in duration.

9.3 Rituximab-hyaluronidase human

Other names: Rituxan Hycela, MabThere S.C.

Product Description: rituximab-hyaluronidase injection is a colorless to yellowish, clear to opalescent solution supplied in sterile, preservative-free, single-dose vials for subcutaneous administration. Each mL of solution contains rituximab (120 mg), hyaluronidase human (2,000 Units), L-histidine (0.53 mg), L-histidine hydrochloride monohydrate (3.47 mg), L-methionine (1.49 mg), polysorbate 80 (0.6 mg), α,α-trehalose dihydrate (79.45 mg), and Water for Injection.

Solution Preparation: Draw up 11.7 mL of rituximab-hyaluronidase injection into a syringe. To avoid clogging, attach administration needle, or catheter, only when the patient is ready for injection.

Storage Requirements: Vials should be stored in the refrigerator at 2˚C–8˚C (36˚F–46˚F) in the original carton to protect from light. Do not freeze.

Stability: If not used immediately, prepared syringe may be stored in the refrigerator at 2-8˚C for up to 48 hours and subsequently for 8 hours at room temp up to 30˚C

Route of administration: Patient must have received at least one dose of rituximab IV, without serious infusion reaction, before starting rituximab- hyaluronidase. DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Premedicate patients with acetaminophen 650mg and diphenhydramine 50mg, prior to each dose.

The dose should be administered over 5 minutes, into the subcutaneous tissue of the abdomen. Never inject into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars. If administration is interrupted, continue administering at the same site, or at a different site, but restricted to the abdomen. Patients must be observed for at least 15 minutes following administration.

Drug Procurement: Rituximab must be obtained from commercial sources.

10.0 CORRELATIVE STUDIES

10.1 Tissue Procurement

The following materials should be sent for each patient that signs consent. The slides should be done after the patient has signed the consent form to participate in the study and within 4 weeks of starting study treatment.

1. Fifteen 4 micron unstained sections on charged (plus) slides
2. Four 10 micron sections (if an incisional or excisional biopsy) or eight 10 micron sections (if needle biopsy) on slides or in a tube

10.2 Blood Sample

20 ml of peripheral blood will be obtained at the time of sample collection (baseline, after C1, and then end of treatment) in heparinized green top tubes.

The green top heparin tubes will be processed into aliquots of plasma and viable mononuclear cells.

10.3 Shipment

Please ship the slides/tube to the Cleveland Clinic Biorepository at the address provided below:

Robert J. Tomsich Pathology and Laboratory Medicine Institute (RT-PLMI)
ATTN: Dr. Genevieve Crane
2119 East 93 Street, L25
Cleveland, Ohio 44106

Please ship the blood samples to the Cleveland Clinic Pharmacology Lab. The Manual of Operating Procedures (MOP) contains more detailed instructions on shipment of the slides and blood samples.

Information about the planned analyses concerning these correlative studies will be added in a protocol amendment.

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters

11.1.1 Screening Evaluation day -28 to 1
Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion. All evaluations must be completed ≤28 days prior to administration of protocol therapy, except where otherwise indicated.

- Informed Consent
- Demographics
- Medical History
- Physical Examination
- IPI score
- Height
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Concurrent Medications Assessment including prescription medications, over-the-counter (OTC) medications and supplements.
- ECOG Performance Status
- Urinalysis
- Baseline Symptoms Assessment
- Complete Blood Count (CBC) with differential
- PT/INR

- Serum chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], and SGPT [ALT]
- Lactate dehydrogenase (LDH) level, uric acid, phosphorus
- Pregnancy test for women of childbearing potential (within 72 hrs of study of study treatment). Women who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential.
- Peripheral blood Epstein Barr Virus (EBV) PCR (if not done within 1 month of diagnosis)
- Remote Hepatitis Panel (Hepatitis B Surface Antigen, Hepatitis B Surface Antibody, Hepatitis B Core Antibody, Hepatitis C antibody)* (no need to repeat if done within 3 months of start of study treatment)
- HIV (no need to repeat if done within 3 months of start of study treatment)
- Electrocardiogram (EKG)
- PET and CT scan of neck, chest, abdomen, and pelvis with IV and PO contrast. Neck CT can be omitted at the investigator's discretion, if no suspicion for involvement. If insurance only allows one type of scan, PET scan is preferred at baseline.
- Bone marrow aspiration and biopsy. This can be omitted at investigator's discretion, if there is low or no suspicion of involvement
- Send tumor biopsy slides to CCF for correlative studies. Biopsy slides should be sent within 4 weeks of start of study treatment. Please see section 10 for detailed information. If tissue is not available, approval from the sponsor-investigator must be received.
- Peripheral blood sample for correlative studies

*** Hepatitis B and C Testing**
Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), anti-HBc, and HCV antibody. In addition, any subjects testing positive for any hepatitis serology must have PCR testing during screening. Subjects with a known history of hepatitis C should be tested for HCV RNA during screening and monthly. See exclusion criterion 4.2.17.

Subjects who are anti-HBc positive should have quantitative PCR testing for HBV DNA performed during screening and may be repeated as per institutional practices. Patients with detectable viral load are not eligible for participation.

11.1.2 Treatment Period
Cycle 1 is 28 days followed by interim response assessment at day 42 (- 3 day window)
Cycle 2 (in patients with CR is 28 days)
Cycles 2-4 (in patients with PR is 28 days)

Cycle 1, Day 1
- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Concurrent Medications Assessment including prescription medications, over-the-counter (OTC) medications and natural/herbal supplements.
- ECOG performance status
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential and platelets.

    - Serum Chemistries: Serum chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]
    - LDH, uric acid, phosphorous
- Rituximab IV administration
- Acalabrutinib started (days 1 – 28)
- Adverse event evaluation and documentation

Cycle 1, Day 8 ± 2 days

- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential
- Rituximab administration
- Adverse event evaluation and documentation

Cycle 1, Day 15 ± 2 days

- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential
    - Serum Chemistries: Serum chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]
- Rituximab administration
- Adverse event evaluation and documentation

Cycle 1, Day 22 ± 2 days

- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential
- Rituximab administration
- Adverse event evaluation and documentation

Cycle 1, Day 42 (-3 day window)

- CT scan of neck, chest, abdomen, and pelvis with IV and PO contrast. CT neck can be omitted if there was no involvement at baseline
- Interim disease response assessment
- Peripheral blood EBV PCR if positive at baseline
- Adverse event evaluation and documentation
- Peripheral blood sample for correlative studies

Cycle 2, Day 1 (for CR responders ONLY)

Cycle 2 should start within 2 weeks after the end of cycle 1 treatment.

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature
- Concurrent Medications Assessment including prescription medications, over-the-counter (OTC) medications and natural/herbal supplements.
- ECOG Performance Status
- Adverse event evaluation and documentation

- Laboratory Studies:
    - Complete Blood Count (CBC) with differential and platelets
    - Serum Chemistries: Serum chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]
    - Lactate dehydrogenase (LDH)
- Rituximab administration on days 1, 8, 15, and 22
- Acalabrutinib on days 1-28

Cycles 2-4, Day 1 (for PR responders ONLY)
Cycle 2 should start within 2 weeks after the end of cycle 1 treatment. There is a ± 3 day window for the start of cycles 3 and 4.

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature
- Concurrent Medications Assessment including prescription medications, over-the-counter (OTC) medications and natural/herbal supplements.
- ECOG Performance Status
- Adverse event evaluation and documentation
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential and platelets
    - Serum Chemistries: Serum chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]
    - Lactate dehydrogenase (LDH) only on cycle 2 day 1 (not required on cycles 3-4)
- Rituximab administration on day 1
- Acalabrutinib started (continue days 1-28)

End of Treatment Response Assessment – 8 weeks ± 7 days after treatment completion (this visit does not apply to subjects with stable/progressive disease after cycle 1)

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Concurrent Medications Assessment including prescription medications, over-the-counter (OTC) medications and natural/herbal supplements.
- ECOG Performance Status
- Adverse Event Evaluation
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential and platelets.
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
    - Lactate dehydrogenase (LDH)
    - Peripheral blood EBV PCR if positive at baseline
- PET and diagnostic CT of neck, chest, abdomen, and pelvis with IV and PO contrast for response assessment. Neck CT can be omitted if no involvement at baseline. If insurance only allows one type of scan, PET scan is preferred for end of treatment assessment.
- Disease response assessment

- Bone marrow aspiration and biopsy if positive at baseline
- Peripheral blood sample for correlative studies

Duration of Follow Up

After completion of the study treatment the subjects will be followed for a total of 3 years. The follow up visits will be done at 6, 12, 18, 24 and 36 months after the last cycle of therapy. There is a ± 14 day window for these visits. If the patient is unable to follow up in person, virtual visits may be used to capture applicable procedures during long-term follow up only.

The follow up visits should include the following:

- Survival/Disease Status
- Physical Examination
- Vital signs
- CBC with differential
- Serum chemistry panel
- Diagnostic CT neck, chest, abdomen and pelvis scan with IV and PO contrast will be done at 6, 12 and 24 months if no disease progression. Neck CT can be omitted if no involvement at baseline
- Peripheral blood EBV PCR if positive at baseline will be done at 6, 12 and 24 months
- Current lymphoma treatment

Patients who have stable/progressive disease are not required to come in for clinical follow up. These patients can be contacted over the phone by the study personnel to obtain the following information

- Survival/Disease Status
- Current lymphoma treatment

Patients will be followed for toxicity until the End of Treatment Response Assessment study visit or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until has been determined that the study treatment or participation is not the cause.

Serious adverse events (SAE) that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

11.2 Calendar

Procedures	Screening	Cycle 1					Cycles 2-4[f]	End of Treatment	Long Term Follow Up (± 14 days)[h]				
	Day -28 to Day 1	Day 1[i]	Day 8 (± 2)	Day 15 (± 2)	Day 22 (± 2)	Day 42 (- 3)	Day 1	8 weeks ± 7 days after treatment completion	6 Months	12 Months	18 Months	24 Months	36 Months
Medical History	X												
Physical Exam	X	X					X	X	X	X	X	X	X
Vital Signs[o]	X	X	X	X	X		X	X	X	X	X	X	X
Height/Weight	X	X					X	X					
Concurrent Meds Assessment	X	X					X						
Baseline Symptom Assessment	X												
Adverse Event Evaluation		X	X	X	X	X	X	X					
Tumor Tissue	X												
Peripheral Blood Sample	X					X		X					
ECOG Status	X	X					X	X					
CBC w/ differential	X	X	X	X	X		X	X	X	X	X	X	X
PT/INR	X												
Serum Chemistry[a]	X	X		X			X	X	X	X	X	X	X
LDH	X	X					X[l]	X					
Uric acid and phosphorous	X	X											
Pregnancy Test	X[g]												
Urinalysis	X												
Hepatitis Panel	X												
HIV testing	X												
EBV PCR	X[j]					X[k]		X[k]	X[k]	X[k]		X[k]	
ECG	X												
CT Neck/Chest/ Abdomen/Pelvis[c]	X[b]					X[e]		X[e]	X[e]	X[e]		X[e]	
PET Scan[c]	X							X					

Bone marrow biopsy/aspiration	X[m]							X[n]					
Disease Response Assessment						X		X					
Acalabrutinib[d]		X					X						
Rituximab		X	X	X	X		X						
Survival/Disease Status									X	X	X	X	X

a. Sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]
b. Neck CT can be omitted at baseline at the discretion of the investigator if there was no suspicion for involvement
c. PET and diagnostic CT scan preferred, but PET alone is preferred, if unable to obtain both.
d. Acalabrutinib given on days 1-28
e. CT neck can be omitted if there was no baseline involvement
f. For subject in a CR after cycle 1, rituximab will be administered on the same schedule as cycle 1 (see Table 2). For these patients, no other study assessment will be done on days 8, 15, and 22.
g. Pregnancy test to be done within 72 hours of starting the study drug. This only applies to women of childbearing potential.
h. Patients with disease progression only need to have survival follow-up and current lymphoma treatment captured (see section 11.1.2). Virtual visits may be used to capture applicable procedures during long-term follow up only if the patient is unable to follow up with the in person.
i. Cycle 1 Day 1 pre-dose assessment do not need to be repeated if being done same day as screening. If the same assessments are being used for both screening and day 1, the data should be entered at screening in the database.
j. EBV PCR at baseline if not done within 1 month of diagnosis
k. EBV PCR if positive at baseline
l. LDH to be done only on Cycle 2 Day 1 (does not apply to Cycle 3 or 4)
m. This can be omitted at investigator's discretion, if there is low or no suspicion of involvement
n. Bone marrow aspiration and biopsy if positive at baseline
o. Blood pressure, pulse, respiratory rate and temperature

12.0 MEASUREMENT OF EFFECT

Response assessments will be evaluated based on Lugano Criteria (refer to Appendix 3). Patients who achieve a CR or PR after cycle 1 treatment will have a CT scan approximately 8 weeks after the end of study treatment. Please see section 11 for the schedule of the imaging studies. Patients will have pre-treatment and end of treatment FDG-PET and/or CT to monitor their response to treatment. For each patient, every effort will be made to use the same radiologic imaging that was obtained at screening to be used to assess response. Interim response will be assessed after cycle 1 using CT scans. During follow up patients will have CT scans done at 6, 12, and 24 months after the last cycle of therapy.

All patients will be evaluable for toxicity from the time of their first treatment with rituximab and acalabrutinib.

The following guidelines are to be used for establishing tumor measurements at baseline and for subsequent comparison:

- The six largest dominant nodes or extranodal masses must be identified at baseline.
- If there are 6 or fewer nodes and extranodal masses, all must be listed as dominant. If there are more than 6 involved nodes or extranodal masses, the 6 largest dominant nodes or extranodal masses should be selected according to the following features:
    - nodes should be clearly measurable in at least two perpendicular measurements
    - nodes should be from as disparate regions of the body as possible
- Measurements for all dominant nodes and extranodal masses will be reported at baseline. Measurements on non-dominant nodes are not required. The lymph nodes or extranodal masses selected for measurement should be measured in two perpendicular diameters, one of which is the longest perpendicular diameter. The lymph nodes should be measured in centimeters to the nearest one tenth of a centimeter (e.g. 2.0 cm, 2.1cm, 2.2 cm, etc.)

12.1 Definitions

12.1.1 Overall Response Rate

Overall response rate (ORR) is defined as all patients that achieve a CR or PR based on end of treatment scans, using the Lugano Criteria.

12.1.2 Complete Remission Rate

Complete response rate (CRR) is defined as all patients that achieve a CR based on end of treatment scans, using the Lugano Criteria.

12.1.3 Partial Remission Rate

Partial response rate (PRR) is defined as all patients that achieve a PR based on end of treatment scans, using the Lugano Criteria.

12.1.4 Duration of Response

Duration of response (DOR) is only measured in responders. DOR is defined as the time from documented response (CR or PR) to the time of confirmed disease progression or death due to any cause, whichever occurs first. Subjects who are still alive and free from progression at the time of data cutoff date, lost to follow-up, have discontinued study, or have initiated other non-protocol anti-tumor therapy (NPT) will be censored at the last tumor assessment when subjects are progression-free.

12.1.5 Progression Free Survival

Progression free survival (PFS) is defined as the time from first dose to documented disease progression, or death from any cause, whichever occurs first. Data for subjects who are still alive and free from progression at the time of data cutoff date, lost to follow-up, have discontinued the study, or have initiated NPT will be censored on last assessment (or, if no post-baseline tumor assessment, at the time of first dose plus 1 day).

12.1.6 Overall Survival

Overall survival (OS) is defined as the time from first dose to death from any cause. Data for subjects who are still alive at the time of data cutoff date, lost to follow-up, have discontinued the study (or, if no post-baseline assessment, at the time of first dose plus 1 day) will be censored on last assessment.

12.1.7 Time to Treatment Failure

Time to treatment failure (event-free survival) is measured from the time from study entry to any treatment failure including discontinuation of treatment for any reason, such as disease progression, toxicity, patient preference, initiation of new treatment without documented progression, or death. This composite endpoint is generally not encouraged by regulatory agencies because it combines efficacy, toxicity and patient withdrawal.

13.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The Adverra EDC™ and OnCore™ databases will be utilized, as required by the Case Comprehensive Cancer Center and Cleveland Clinic, to provide data collection for both accrual entry and trial data management. Adverra EDC and OnCore™ are Clinical Trials Management Systems housed on secure servers. Access to data through Adverra EDC and OnCore™ is restricted by user accounts and assigned roles. Once logged into the Adverra EDC or OnCore™ system with a user ID and password, Adverra EDC™ and OnCore™ define roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu for OnCore™ access, and taussigoncore@ccf.org for Adverra EDC™ access.

Adverra EDC™ is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. When properly utilized, Adverra EDC™ is 21 CFR 11 compliant. This study will utilize electronic Case Report Form completion in the Adverra EDC™ database. A calendar of events and required forms are available in Adverra EDC™.

13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue

from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

14.0 STATISTICAL CONSIDERATIONS

14.1 General Considerations

This is an open-label, single-arm, phase II trial of Rituximab in combination with Acalabrutinib treating newly diagnosed B cell post-transplant lymphoproliferative disorder. The primary objective is to assess the efficacy of the combination regimen. The primary endpoint is overall response rate (ORR) 8 weeks after treatment completion. Secondary endpoints include complete response rate (CRR), partial response rate (PRR), duration of response (DoR), overall survival (OS), progression-free survival (PFS), time to treatment failure (TTF) and toxicity profile.

14.2 Rational for Sample Size

The null ORR of single agent Rituximab is 60% based on literature [6-11]. We expect the ORR (CR +PR) of combination regimen be at least 75%. Using one-sample exact binomial test, 62 patients will ensure a power of 80% at two-sided type I error rate of 10% to detect such a difference. The trial will be considered a success if 44 or more CRs/PRs are observed out of 62 patients.

14.3 Futility Monitoring Rule

We expect the ORR of Rituximab + Acalabrutinib will be 15% or higher than Rituximab alone. We will monitor the ORR and stop the trial early for futility if observed ORR is unlikely to achieve the target (75%). A Bayesian method [31] will be used to monitor futility. The reference ORR was assumed to follow a Beta(60,40) distribution, which corresponds to an expected ORR of 60% with an effective sample size of 100. The prior distribution of true ORR was set as Beta(0.6,0.4), which also has an expected ORR of 60%, but with an effective sample size of 1. Futility monitoring will start from the 10th patient and in cohorts of 10 thereafter. We will stop the trial early if Pr (ORR < 0.60 + 0.15|data) > 0.9, i.e. stop the trial early if the posterior probability of experimental ORR missing target (75%) is high (>0.9) given data. Table 5 summarizes early stopping boundaries, and table 6 summarizes operating characteristics.

Table 5. Summary of futility stopping boundaries using Bayesian monitoring rule. Futility monitoring will start from the 10th patient and in cohorts of 10. Trial will stop early if the number of CRs/PRs observed is less than or equal to the boundaries. For example, if we observed 5 or less CRs/PRs out of the first 10 patients, we will stop the trial early. Similarly, if we observed less than or equal to 12/20, 18/30, 25/40, or 32/50 CRs/PRs, we will stop the trial early for futility.

Total Number of Patients Treated	10	20	30	40	50
Number of CRs/PRs Observed <=	5	12	18	25	32

Table 6. Summary of operating characteristics based on 10,000 simulations using early stopping boundaries in table 5. E.g. If the true ORR is 75%, the early stopping probability is 0.17; if the true ORR is 60% (same as Rituximab alone), the early stopping probability is 0.84; if the true ORR is 50% (worse than Rituximab alone), the trial will stop early with probability 0.99. MultcLean v2.1 from MDACC was used to calculate the stopping boundaries and operation characteristics

Scenario	True ORR	Pr(Early Stopping)	Average #Patients Enrolled	Average #CR/PR Observed
1	0.80	0.06	57.5	46.0
2	0.75	0.17	53.0	39.8
3	0.60	0.84	26.9	16.1
4	0.50	0.99	15.9	7.9

14.4 Toxicity Monitoring

Toxicity is defined as any grade 4 adverse event or treatment related death. We will do interim looks for toxicity after every 15 patients have been treated and assessed for toxicity. If the estimated toxicity rate is higher than 20%, we will pause the study and a comprehensive safety assessment will be performed.

14.5 Analysis Populations

All efficacy and safety analysis will be performed using the treated population, which consists of all subjects who receive any amount of study treatment. The analysis of DOR will only include subjects who have achieved objective response and will be measured from the first observation of DOR until date of progressive disease.

14.6 Missing Data Handling

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

14.7 Endpoint Data Analysis

Patient characteristics will be summarized using mean, SD, range, frequencies, and percentages where appropriate. ORR will be estimated along with 90% CIs, and compared against the null using exact binomial test. Logistic regression model will be used to identify factors associated with response status. Survival endpoints will be estimated using Kaplan-Meier method and compared using log-rank test. Cox proportional hazard model will be used to identify factors associated with survival endpoint. Other analyses will be carried out as appropriate.

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APPENDIX 1

Performance Status Criteria [29]

ECOG Performance Status Scale	
Grade	Description
0	Normal activity. Full 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% if 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 2

Known Strong in Vivo Inhibitors or Inducers of CYP3A

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

a. A strong inhibitor is defined as an inhibitor that increases the AUC of a substrate by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. Withdrawn from the United States market because of safety reasons.
d. A strong inducer is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate.
e. 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 Sponsor 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

APPENDIX 3

Assessment of Responses based on Lugano Criteria as defined by Cheson et al [30]

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

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

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

APPENDIX 4

Cockcroft Gault Formula to Estimate Renal Function Using Serum Creatinine

Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$\text{CLcr (ml.min)} = \frac{[140\text{-age (years)}] \times \text{weight (kg)} \times [0.85 \text{ if female})}{72 \times \text{serum creatinine (mg/dL)}}$$

Reference:
1. Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. Nephron. 16:31-41.

APPENDIX 5

Subject Pill Diary

Subject Name _____ Subject Study ID _____ Today's date ___/___/___
Drug _____ Cycle #:

INSTRUCTIONS FOR THE SUBJECT:

1. Complete one form every 4 weeks (one treatment cycle).
2. You will take one Acalabrutinib capsule twice each day about 12 hours apart. Take the capsules with a full glass (8 oz) of water and with or without food, as you wish. If a dose is missed by more than 3 hours, please skip that dose and take the next dose at the next scheduled time.
   Morning dose: take # of ____ mg capsule
   Evening dose: take # of ____ mg capsule
3. Record the date, the number of capsules ***of each size*** that you took, and what time you took them.
4. If you have any comments or notice any side effects, please record them in the "Comments" column.
5. Please bring this form and your bottle**(s)** of acalabrutinib to your physician when you return for each appointment.
6. Please sign your name at the bottom of the diary.

Day	Date	Time of morning dose	# of capsules taken			Time of evening dose	# of capsules taken			Comments
			___ mg	___ mg			___ mg	___ mg		
1										
2										
3										
4										
5										
6										
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Subject's Signature: _____ Date: _____

Reviewed by Signature:	**Date:**

Date: _____

Date: _____