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A Phase 2, Open-Label Study of Acalabrutinib in Combination with R-ICE For Relapsed or Refractory Non-Germinal Center Diffuse Large B Cell Lymphoma, Transformed Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia or Transformed Marginal Zone Lymphoma

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Funding Collaborator	AstraZeneca
Study Drug Name	Acalabrutinib
Version	3.0
Version Date	24 June, 2021

LIST OF STUDY CENTERS

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Funding Collaborator	AstraZeneca

INVESTIGATOR AGREEMENT

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol.

I have read and understand the information in the Investigators' Brochure (and/or other such pertinent safety information) regarding the risks and potential benefits.

I agree to inform all those who assist/collaborate with me in the conduct of this study of their responsibilities and obligations.

Once the protocol has been reviewed and approved by the Institutional Review Board (IRB) I understand that any change(s) made during the course of the study must also (first) be approved by the IRB prior to implementation, except when such modification is made to remove any immediate hazard(s) to the subject(s).

I certify that I and the study staff responsible, have received the requisite training to conduct this research protocol.

I agree to maintain adequate and accurate records in accordance with the University of Miami policies, federal, state and local laws and regulations.

I agree to maintain the confidentiality of all information received and/or developed in connection with this protocol.

eProst Number: 20190706	
Protocol Version Number: 3.0	**Protocol Version Date: 24 June, 2021**

Signature of Investigator:	**Date:**
Name of Investigator (printed):	**Institution:**

PROTOCOL REVISION HISTORY

Version Number	Version Date	Summary of Revisions Made
2.0	8 June, 2020	1. Section 1.4.2.1-1.4.2.5 was updated with the latest language from the Investigational Brochure, version 9.0, dated 19 February, 2020. 2. Section 3.10.3:The old version of contraception language was replaced with the latest version of contraception template language from the HSRO published ICF template. 3. Section 4.0 Replaced incorrect reference from “Section 3.4” to “Section 3.5” 4. Section 4.1.7 Added directed physical exam to be performed every day while participants are receiving R-ICE treatment. 5. Section 4.1.11 Added that chemistry (potassium) will be performed every day while participants are receiving R-ICE treatment 6. Section 4.1.12 Added that urinalysis will be performed every day while participants are receiving R-ICE treatment. 7. Appendix 1: • Added a treatment window of day 1+ 7 or – 3 days to Cycles 2-3 • Added treatment window of 14-28 days to end of treatment visit • Added a treatment window of + or – 1 week to the follow up visits that will be performed every 12 weeks • Replaced reference of Section 3.4 to Section 3.5.3 • Added chemistry (potassium) • Added urinalysis • Added footer for directed physical exam, chemistry and urinalysis to be performed every day while participants are receiving R-ICE treatment. 8. Appendix 5: Added instructions on taking medication to the patient diary 9. Appendix 6 Collection and processing of pre-treatment and end of treatment blood samples for BCR clonotyping was added.
3.0	24 June, 2020	Global Changes • Replaced “sponsor-investigator” with “lead investigator” and clarified that each site sub-investigator was the “study site principal investigator”. • Clarified that the University of Miami is the coordinating study center. • Replaced “investigational drug sponsor” with “supplier of the study medication” Changes to Specific Sections: 1. Section 3.0. Added language to indicate that this is a multi-center, open-label, single arm trial. 2. Section 3.1.3. References to MedRA were removed and replaced with NCI CTCAE 5.0. 3. Section 3.3.3. Added recruitment and enrollment language, consistent with the local addendum language. 4. Section 3.4. Added definitions for participant discontinuation procedures and criteria and definitions for patients lost to follow up. 5. Section 3.14. Added standard study auditing and monitoring language.

		6. Sections 6.2.5, 6.2.6, 6.2.7. Updated AE/SAE reporting requirements for study sites to UM (coordinating center), coordinating center requirements to the FDA and pharmaceutical company. 7. Section 7.4. Added references to the manual of procedures.

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ABBREVIATIONS

λ_z	terminal elimination rate constant
AE	adverse event
AESI	adverse events of special interest
Akt	protein kinase b
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice per day (dosing)
BOR	best overall response
BTK	Bruton tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CD	cluster of differentiation (cell surface marker)
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CIs	confidence intervals
CL/F	oral clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
COPD	chronic obstructive pulmonary disease
CR	complete response (remission)
CRF	case report form
CSSF	Clinical Supplies Shipping Receipt Form
CT	computed tomography
ctDNA	circulating tumor DNA
CTCAE	Common Terminology Criteria For Adverse Events
CTLA-4	cytotoxic t-lymphocyte-associated protein 4
CYP	cytochrome p450
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
IEC	independent ethics committee
Ig	Immunoglobulin
IRB	institutional review board
ir	immune-related
irAE	immune-related adverse event
irRECIST	immune-related response criteria
IV	intravenous or intravenously
Jak	Janus kinase
LDH	lactate dehydrogenase
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
MDSC	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MTD	maximum tolerated dose
MTV	metabolic tumor volume
mTOR	mammalian target of rapamycin
NE	Nonevaluable
NGS	next-generation sequencing
NK	natural killer (cells)
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PFS	progression-free survival
PD	pharmacodynamic, pharmacodynamics, or progressive disease
PD-1	programmed death-1 (receptor)
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2
P-gp	p-glycoprotein 1 (transporter)
PI3K	phosphatidylinositol-3 kinase
PK	pharmacokinetic or pharmacokinetics
PP	per protocol
PR	partial response (remission)
Q3M	every 3 months
Q3W	every 3 weeks
Q12W	every 12 weeks
QD	once per day (dosing)
QT_c	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease or standard deviation

SUSAR	suspected unexpected serious adverse reaction
Syk	spleen tyrosine kinase
$t_{½}$	terminal elimination half-life
T3	Triiodothyronine
T4	Thyroxine
TAM	tumor-associated macrophage
T_{max}	time to maximum concentration
TSH	thyroid-stimulating hormone (thyrotropin)
T_{reg}	regulatory T cells
ULN	upper limit of normal
V_z/F	oral volume of distribution
WHODRUG	World Health Organization Drug Dictionary

STUDY SYNOPSIS

Study Title	A Phase 2, open-label study of acalabrutinib in combination with R-ICE for relapsed or refractory non-germinal center diffuse large B cell lymphoma, transformed chronic lymphocytic leukemia/small lymphocytic leukemia or transformed marginal zone lymphoma
Protocol Number	20190706
Study Drug	ACALABRUTINIB (ACP-196), rituximab, ifosfamide, etoposide, carboplatin
Phase	2
Coordinating and Study Center	Sylvester Comprehensive Cancer Center
Additional Study Centers	• Moffitt Cancer Center • City of Hope
Study Objectives	**Primary Objective** • Improve complete remission (CR) rate of R-ICE for rel/ref non-GC DLBCL and transformed histologies from 29% to 50% with acalabrutinib + R-ICE for 3 cycles by RECIL.[1] **Secondary Objectives** • Safety and tolerability of acalabrutinib with R-ICE in patients with rel/ref DLBCL • (partial remission) PR, CR, overall response rate (ORR) of acalabrutinib + R-ICE • Ability to mobilize $\geq$ 2 x10^6 CD34+ cells/kg • Event-free survival (EFS), progression-free survival (PFS) and overall-survival (OS) at 1 year **Exploratory Objective** • Correlate efficacy endpoints (ORR, PFS, OS) with: baseline metabolic tumor volume (MTV), circulating cell-free tumor DNA (ctDNA), and the results of next-generation sequencing (NGS) of tumor. NGS in diagnostic biopsy if available.
Study Design	This is a phase II study of acalabrutinib in combination with R-ICE in rel/ref non-GC DLBCL per Hans criteria,[2] Each cycle will begin day 1 and last for 21 days. Acalabrutinib will be administered day 1-21 of every cycle for 3 cycles, in conjunction with 3 cycles of R-ICE. R-ICE will be administered per standard institutional policy. In addition to a baseline PET-CT scan, confirmatory scans will be obtained post cycle 2 per cross sectional imaging criteria by CT and post cycle 3 per RECIL criteria.[1] If patients have progressive disease after cycle 2, they will be removed from study treatment. An EOT (EOT) visit within 14 days of the last dose of study drug is required for any patients who permanently discontinue study drug for any reason, including disease progression. Patients will then be followed for 52 weeks for EFS, PFS, and OS after removal from or completion of study treatment, or until death, whichever occurs first. Patients removed from study treatment for adverse events will be followed until resolution or stabilization of the adverse event.

Efficacy and Safety Parameters	**Efficacy Parameters** EFS, PFS, OS **Safety Parameters** The safety of acalabrutinib in combination with R-ICE will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment emergent AEs or abnormalities of laboratory tests; SAEs; DLTs, or AEs leading to discontinuation of study treatment, or death. For consistency of interpretation, AEs and laboratory results will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the severity of AEs and selected laboratory parameters will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.
Pharmacodynamic, Pharmacokinetic and Biomarker Parameters	Exploratory correlative studies may include characterization of tumor subtypes by NGS, including comparing pre- and post- study treatment biopsies in patients without a clinical response and/or progression of disease.[31] Baseline and end of treatment (EOT) PET scan will be assessed for response by MTV as a correlative biomarker.
Sample Size	In the first stage, we will enroll 20 eligible patients. If 6 or fewer patients achieve CR after 3 cycles, no additional patients will be enrolled. If 7 or more patients achieve CR, then an additional 26 patients will be enrolled for the second stage.
Inclusion Criteria	1. Men and women ≥ 18 years of age. 2. Patients must have histologic confirmation of relapsed or refractory lymphoma. 3. Baseline FDG-PET scans must demonstrate positive lesions compatible with CT defined anatomical tumor sites.[26] a) CT scan showing at least: i) 2 or more clearly demarcated lesions/nodes with a long axis >1.5cm and short axis ≥1.0cm, or ii) 1 clearly demarcated lesion/node with a long axis >2.0cm and short axis ≥1.0cm. 4. Patient must have been previously treated for B cell non-Hodgkin lymphoma with any of the allowable below: a) First-line treatment with rituximab and an anthracycline-based chemotherapy. b) Monotherapy rituximab, dosed prior to first-line rituximab combined with anthracycline containing chemotherapy, or as maintenance therapy. c) Radiotherapy as part of the first-line treatment plan including anthracycline and rituximab. 5. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 (See Appendix 2) 6. Life expectancy of greater than 6 weeks. 7. Patients must have normal organ and marrow function as defined below, a) absolute neutrophil count ≥1000/mcL (unless due to lymphoma involvement of the bone marrow)

	b) platelets ≥75,000/mcL (unless due to lymphoma involvement of the bone marrow) c) total bilirubin ≤ 1.5 x within normal institutional limits (unless due to lymphoma involvement of liver or a known history of Gilbert's disease) d) AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal (unless due to lymphoma involvement of liver) e) creatinine within normal institutional limits, or f) creatinine clearance ≥40 mL/min/1.73 m2 for patients with creatinine levels above institutional normal. (unless due to lymphoma) 8. Major surgical procedure within 28 days of first dose of study drug. 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. 9. Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of acalabrutinib + R-ICE. 10. Men who are sexually active and can beget children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of acalabrutinib + R-ICE. 11. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of study drug. 12. Willing and able to participate in all required evaluations and procedures in this study protocol, including swallowing capsules without difficulty. 13. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations).
Exclusion Criteria	1. Germinal-center cell-of-origin DLBCL 2. Patients who have had chemotherapy or radiotherapy < 21 days prior to first administration of study treatment or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. 3. Patients who are receiving any other investigational agents. 4. Patients with known central nervous system involvement of lymphoma. 5. History of allergic reactions attributed to compounds of similar chemical or biologic composition to acalabrutinib or R-ICE with the exception of first-infusion reaction to rituximab. 6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. Recent infections requiring systemic treatment need to have completed therapy > 7 days before the first dose of study drug. 7. Pregnant women are excluded from this study because an acalabrutinib R-ICE is a chemotherapy program with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with acalabrutinib R-ICE, breastfeeding should be discontinued if the mother is treated with acalabrutinib R-ICE.

	8. HIV-positive patients on combination antiretroviral therapy are eligible, unless the patient's CD4 count is below the institutional lower limit of normal, or the patient is taking prohibited CYP3A4/5 strong inhibitors or inducers. 9. Patients may not have received any anti-cancer therapy for their primary rel/ref DLBCL with the exception of palliative RT. 10. Uncontrolled Autoimmune Hemolytic Anemia or ITP resulting in (or as evidenced by) declining platelet or Hgb levels within the 4 weeks prior to first dose of study drug. 11. Presence of transfusion-dependent thrombocytopenia. 12. Prior exposure to a BTK inhibitor. 13. History of prior malignancy, with the exception of the following: a) Malignancy treated with curative intent felt to be at low risk for recurrence by treating physician b) Adequately treated non-melanomatous skin cancer or lentigo maligna melanoma without current evidence of disease c) Adequately treated cervical carcinoma in situ without current evidence of disease. 14. Currently active clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification, or history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to first dose with study drug. 15. Unable to swallow capsules, or disease significantly affecting gastrointestinal function or, resection of the stomach or small bowel, malabsorption syndrome or symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction. 16. Serologic status reflecting active hepatitis B or C infection. Patients that are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody will need a negative polymerase chain reaction (PCR) prior to enrollment. (PCR positive patients will be excluded.) Hepatitis C antibody positive patients are eligible if PCR is negative. Hepatitis B core antibody (+) patients without evidence of HBsAg or Hep B PCR (+) are eligible with appropriate Hepatitis B reactivation prophylaxis. 17. History of stroke or intracranial hemorrhage within 6 months prior to enrollment. 18. Current life-threatening illness, medical condition, or organ system dysfunction which, in the Investigator's opinion, could compromise the patient's safety, or put the study at risk. 19. Received anticoagulation therapy with Coumadin or equivalent vitamin K antagonists within the last 28 days. 20. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug. 21. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4), grade ≤1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia. 22. Known bleeding disorders (e.g., von Willebrand's disease), elevated PT/INR/aPTT > 2x normal, active bleeding or hemophilia.

	23. Unwilling or unable to participate in all required study evaluations and procedures. 24. Currently active, clinically significant hepatic impairment (≥ moderate hepatic impairment according to the NCI/Child Pugh classification. 25. Breastfeeding or pregnant. 26. Concurrent participation in another therapeutic clinical trial. 27. Patients who require proton pump inhibitors at baseline (prior to fist dose of study drug) or strong CYP3A4 inhibitor or inducer and are not able to switch to another medication
Dose Regimen/Route of Administration	Acalabrutinib is provided as hard gelatin capsules for oral administration approximately every 12 hours. R-ICE will be administered as per standard institutional policy.
Concomitant Medications	**Permitted Concomitant Therapy** Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted as per institutional standards. Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines. [3] Transfusions may be given in accordance with institutional policy. Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted. Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100 mg per day of prednisone or equivalent. The following may be considered: localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies. **Prohibited Concomitant Therapy** The concomitant use of strong inhibitors/inducers of CYP3A4 (see Appendix 3) should be avoided when possible (see Section 3.10.2). If a subject requires a strong CYP3A inhibitor while on study, monitor the subject closely for potential toxicities. For additional information on drugs with potential drug-drug interactions, refer to Section 3.10.2. Any non-study related chemotherapy, anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone > 20 mg/day for longer than 2 weeks), experimental therapy, or radiotherapy for treating DLBCL are prohibited. Warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) are prohibited.

	Acalabrutinib and Concomitant Therapy The effect of agents that reduce gastric acidity (eg, proton pump inhibitors, H2-receptor antagonists or antacids) on acalabrutinib absorption was evaluated in a healthy volunteer study. Results from this study indicate that subjects should avoid the use of calcium carbonate containing drugs or supplements for a period of at least 2 hours before and 2 hours after taking acalabrutinib, and acalabrutininb should be taken 2 hours before short-acting H2-receptor antagonists. Use of omeprazole or esomeprazole or any other proton pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. However, if a subject must take a proton pump inhibitor (for example, for an ulcer that develops on study), please discuss treatment options with the medical monitor.

1 BACKGROUND INFORMATION

1.1 SALVAGE THERAPY FOR AUTOLOGOUS STEM CELL TRANSPLANT ELIGIBLE PATIENTS WITH REL/REF DLBCL

The standard treatment for relapsed or refractory (rel/ref) diffuse large B-cell lymphoma (DLBCL) is high-dose chemotherapy followed by autologous stem cell transplantation (HDT/ASCT)[4], provided that chemosensitive disease is established with salvage therapy (ST). With the use of modern supportive care, transplant-related mortality is minimal and long-term event-free survival (EFS) is approximately 50%, with variability attributable to pre-transplantation prognostic factors. For the past decade, the lymphoma service at MSKCC has defined pre-treatment clinical and biologic prognostic factors in the setting of ICE[5,6], the most commonly used ST program in the world which was developed at MSKCC.

It has been recognized that the most important factor predictive of outcomes for rel/ref DLBCL prior to ASCT is the depth and quality of response to ST[5,7-10]. In the pre-rituximab era, our group reported the initial ICE experience for rel/ref non-Hodgkin lymphoma, the vast majority of the patients (72%) having DLBCL. The overall response rate (complete [CR] or partial [PR] remission) was 66.3% [5]. Those patients in CR at the time of ASCT had significant improvement in EFS compared to those in PR, 54% compared to 29% at 40 months ($p < 0.001$). Sequentially, our group reported significant improvement in CR to ST compared to historical controls with the incorporation of rituximab into the ICE program, 53% CR with R-ICE compared to 27% CR with ICE alone[11]. Of particular importance, none of the patients received rituximab with initial anthracycline-based combination chemotherapy; thus were “rituximab-naïve” at the time of R-ICE ST. Recently, the large, multi-institutional international Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) trial comparing R-ICE to R-DHAP demonstrated no difference in response rate between the two ST arms[12]. Disappointingly, the overall response rate was 63% with a CR/CRu rate of 38% with no difference between R-DHAP and R-ICE; much lower than previous rituximab-naïve historic controls. Of importance, patients previously exposed to rituximab experienced a CR/CRu rate of 29% on the CORAL study (personal communication, Gisselbrecht). These poor results were further translated to a disappointing 53% EFS at 3 years for chemosensitive patients who proceeded to ASCT, and a sobering 31% EFS at 3 years by intent-to-treat. Clearly, the magnitude of benefit rituximab added to previously rituximab-naïve rel/ref patients has been nearly completely blunted in the current-era of ubiquitous rituximab exposure during initial induction chemotherapy in rel/ref patients. Given that the most significant prognostic factor prior to ASCT for rel/ref DLBCL is CR rate, the need for improvement in efficacy of ST is of utmost importance to outcomes in rel/ref DLBCL going forward.

1.2 BRUTON TYROSINE KINASE INHIBITION IN B CELL LYMPHOMAS AND DLBCL, INCLUDING COMBINATION WITH R-ICE

BTK is a tyrosine kinase involved in B cell signaling through the B cell receptor (BCR)[13]. The importance of this signaling pathway in normal B cell function is evidenced by X-linked agammaglobulinemia (XLA) where mutation in the BTK gene results in the absence of mature B cells and subsequent function. The primary function is antigen receptor signaling in B cells, where it is preferentially expressed compared to other lymphocytes (ie T cells and natural killer (NK) cells). In XLA, there are no demonstrable quantitative or qualitative T cell and NK cell defects.

There is emerging evidence of the importance of signaling through BTK in propagating B cell lymphomas. The expression of a functional BCR is maintained during progression of B cell lymphoma.[14] Additionally, the knockdown of BCR proteins by RNA interference results in apoptosis of multiple B cell lymphoma lines.[15]

Recently, the pathogenic chronic activation of BCR has been critical in cell survival of activated B-cell like (ABC) phenotype of DLBCL.[16,17] This subtype of DLBCL has demonstrated poor-response to

initial induction therapy,[18] and thus represents the largest subset of patients with rel/ref DLBCL.[19] In ABC phenotypic cell lines of DLBCL, short-hairpin inhibition of RNA (shRNA) involved in BCR receptor signaling resulted in apoptosis in cells that possessed wild-type (WT) CARD11.[17] Roughly 90% of ABC DLBCLs have WT CARD11.[17] WT BTK is a key proximal kinase in the BCR signaling pathway which, upon activation via BCR, phosphorylates downstream to NF-κB resulting in cell survival.

1.2.1 BTK inhibition with ibrutinib as a single agent in DLBCL

Most recently a multi-center phase II study of single-agent ibrutinib administered at a dose of 560 mg PO daily for rel/ref DLBCL was reported[20]. Tolerability in 80 evaluable patients was similar to the original phase I study with no new safety concerns. The overall response rate (ORR) was 25% (20/80). Importantly, ORR was 37% in ABC-subtype patients with median response duration of 4.8 months. One of 20 GCB-subtype patients responded to therapy, thus conferring the ABC-subtype selectivity for the BTK-dependent mechanism of action of ibrutinib.

1.2.2 R-ICE for relapsed and refractory B cell lymphoma

As R-ICE has been compared to R-DHAP in the salvage setting without demonstrable difference in response rates as mentioned above,[12] R-DHAP was associated with significantly more grade 3 to 4 hematologic and non-hematologic toxicity. Most notably, 6% grade 4 nephrotoxicity was seen in the R-DHAP group compared to 1% in the ICE group.[12] This is attributable to the nephrotoxicity of cisplatin in the R-DHAP regimen. This nephrotoxicity can have critical implications to further therapy; including allogeneic stem cell transplantation wherein the use of potentially nephrotoxic calcineurin-inhibitor based graft-versus-host disease prophylaxis may be contraindicated. Perhaps more importantly, the Bio-CORAL correlative study suggested a potential signal of improved chemosensitivity with R-ICE compared to R-DHAP in ABC-subtype rel/ref DLBCL by gene expression profiling.[19] This provides clear rationale for selectively studying R-ICE in ABC-subtype rel/ref DLBCL in combination with the selective BTK inhibitor iburitinib.

1.2.3 Phase I ibrutinib + R-ICE

In this phase I a standard 3 x 3 dose escalation of ibrutinib at 420 mg (dose level [DL] #1), 560 mg (DL #2) and 840 mg (DL #3) days 1-21 with R-ICE for 3 cycles, every 21 days for rel/ref DLBCL, all cells of origin and phenotypes including transformed histologies.[29] The primary objective was to determine safety and the maximum tolerated dose (MTD) of ibrutinib with R-ICE. Secondary objectives included response rate according to CT and PET per Deauville score (DS). Twenty-one patients at a median age of 59 years (range 19-75 years). There were no dose-limiting toxicities (DLTs) seen at DL #1 (n=3), 2 (n=3), or 3 (n=15). One patient was removed for rapid progression of disease and was not evaluated for toxicity or response without completing one cycle of therapy, though was graded as an event in KM calculations. Ninety-four percent (15/16) of patients experienced expected and transient grade 3 or 4 hematologic toxicities with hematopoietic recovery prior to each cycle. The median number of cumulative platelet transfusions per patient over 3 cycles was 2 (range 0-11). Eleven of the 16 patients evaluable for response underwent chemotherapy-primed CD34+ hematopoietic progenitor cells (HPCs) apheresis procedures on study; 10 of the 11 patients successfully collected HPCs with a median of 5.6 x 10^6 CD34+/kg (range 1.7-8.6). The only patient that failed to collect HPCs was an HIV(+) patient at DL #3 in the setting of febrile illness. One patient with non-GCB DLBCL experienced grade 3 atrial fibrillation/flutter during cycle #1 and was subsequently removed from study per the treating physician's decision. This patient was evaluable toward response and survival by ITT. Other notable events on study include: one patient removed following end-of-cycle #2 for asymptomatic pneumatosis coli on restaging imaging (CR) and one patient that self discontinued study for grade 2 nausea following cycle #2 also a CR. Both of these patients proceeded to HDT-ASCT and remain progression-free.

Efficacy

Of the 20 patients evaluable for a response, 11 achieved and CR and 7 achieved a PR for an overall response rate of 90%. By ITT, 8/9 patients with non-GC DLBCL achieved a CR (89%), with one aforementioned patient removed from study for toxicity (grade 3 atrial fibrillation). Thus, all 8 patients with non-GC DLBCL that completed 3 cycles of therapy achieved a complete metabolic remission. Additionally, all 5 patients with rel/ref Richter's transformed CLL/SLL achieved a response (CR=2, PR=3). In univariate analysis, rel/ref non-GC DLBCL demonstrated a significantly increased rate of CR compared to other subtypes (p = 0.008).

At a median follow-up of 14 months for survivors, the one-year event-free (EFS), progression-free (PFS) and overall survival (OS) by ITT was 0.51 (95% CI: 0.33-0.79), 0.62 (95% CI: 0.43-0.9) and 0.65 (95% CI: 0.46-0.93), respectively. Of the 18 patients that achieved a response on study, n=14 and n=2 proceeded to HDT-ASCT and allogeneic hematopoietic transplantation (allo-HCT), respectively. The one-year PFS and OS of transplanted patients on study are 0.73 (95% CI: 0.51-0.99) and 0.82 (95% CI: 0.62-0.99), respectively.

1.3 ACALABRUTINIB (ACP-196)

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. 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 MCL who have received at least 1 prior therapy. It is also being evaluated for the treatment of patients with other B-cell malignancies.

1.3.1 Mechanism of Action

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.[30] Functional inhibition of non-target cells (eg, T cells, NK cells, platelets) was not observed for acalabrutinib at clinically relevant concentrations.

In Table 1-1 the group of 3F-Cys kinases are listed with the IC_{50} for acalabrutinib and ibrutinib. For acalabrutinib, the strongest inhibition was observed for Btk with less activity against Tec, Bmx, and ErbB4. However, ibrutinib showed inhibition of all 10 kinases. One kinase potently inhibited by ibrutinib is EGFR, which may explain the ibrutinib-related incidence of diarrhea and rash reported for ibrutinib in clinical trials of hematologic malignancies (IMBRUVICA prescribing information).

Table 1-1. Potency of acalabrutinib and Ibrutinib on Group of 3F-Cys Kinases

	IC_{50} (nM)	
	Acalabrutinib[1]	**Ibrutinib[2]**
Btk	3.1	0.5
Tec	29	78
Bmx	39	0.80
Itk	>1000	10.7
Txk	291	2.0[1]
EGFR	>1000	5.6
ErbB2	912	9.4
ErbB4	13.2	2.7[1]
Blk	>1000	0.5
Jak3	>1000	16.1

IC_{50} = inhibitory concentration causing half-maximal inhibition
Profiling at Life Technology
Honigberg 2010; ibrutinib data for Txk and ErbB4 profiled at Life Technology

1.3.2 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile; for detailed information on the safety pharmacology of acalabrutinib, refer to the Investigator Brochure.

1.3.3 Drug-drug Interaction Potential

For more detailed information on drug-drug interaction potential for acalabrutinib, refer to the Investigator Brochure.
Please refer to Section 3.9.2 for guidance on drugs that may cause drug-drug interactions.

1.4 CLINICAL EXPERIENCE – ACALABRUTINIB

For more detailed information on the clinical experience for acalabrutinib, please refer to the Investigator Brochure.

1.4.1 Clinical Efficacy –

In study LY-002, a phase Ib study of single-agent acalabrutinib for B cell lymphomas, in non-GCB DLBCL (by IHC), n=21, responders n = 5 (24%, 3 ABC, 1 GCB, and 1 indetermined by NanoString). The CR rate was 19%. The ORR for patients with ABC-subtype (non-GCB) by NanoString was 33% (3/9) with 22% (2/9) achieving a CR. The most common ≥ grade 3 adverse event was anemia. Median steady-state BTK target occupancy was 97-99% in 5 patients analyzed at acalabrutinib 100 mg orally twice-daily. (Dyer et al ASCO Annual Meeting 2018 abstract #7547).
This section briefly summarizes data from ACE-CL-001 (NCT02029443), an ongoing non-randomized, sequential group, dose-escalation Phase 1/2 study in subjects with relapsed/refractory or previously untreated chronic lymphocytic leukemia (CLL), Richter's syndrome, or prolymphocytic leukemia. Acalabrutinib has been well tolerated at all dose levels evaluated. No DLTs have occurred at any dose level. The MTD was not reached in this study, and the dose escalation was stopped at 400 mg. Preliminary Day 1 PK data revealed variable and dose-linear PK. There was no accumulation of acalabrutinib in plasma upon repeat dosing. For detailed information on the safety and PK of acalabrutinib, refer to the Investigator Brochure.
Preliminary PD data from ACE-CL-001 show that Btk occupancy with acalabrutinib, in peripheral blood cells, is ≥ 90% at 4 hours after dosing but declines over 24 hours with QD dosing, while with 100 mg BID dosing, full Btk occupancy (94% to 97%) is maintained over 24 hours. These data suggest that synthesis of de novo Btk may occur within 24 hours.

1.4.2 Adverse Events –

Safety analysis of acalabrutinib monotherapy was conducted to assess safety for acalabrutinib-exposed subjects with hematologic malignancies without confounding toxicity from combination therapy drugs. Overall, the safety of monotherapy acalabrutinib in subjects with hematologic malignancies has been acceptable in the integrated analysis – refer to section 6.3.1 of the Investigator Brochure 9.0.

1.4.2.1 *Hemorrhage*

Serious hemorrhagic events, including fatal events, have occurred in clinical studies with acalabrutinib (see Table 24 of the Investigator's Brochure).
The mechanism for hemorrhage is not well understood. Patients receiving antithrombic agents may be at increased risk of hemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary. Consider the benefit-risk of withholding acalabrutinib for at least 3 days pre- and post-surgery.

Subjects with hemorrhage should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.

1.4.2.2 *Infection*

Serious infections (bacterial, viral, and fungal) including fatal events, have occurred in clinical studies with acalabrutinib. The most frequently reported Grade ≥3 infection was pneumonia (preferred term). Across the acalabrutinib clinical development program (including subjects treated with acalabrutinib in combination with other drugs), cases of hepatitis B virus reactivation, aspergillosis, and progressive multifocal leukoencephalopathy (PML) have occurred (see Table 24 of the Investigator's Brochure).

Consider prophylaxis in patients who are at increased risk for opportunistic infections. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate. Subjects with infection events should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated.

1.4.2.3 *Cytopenias*

Grade 3 or 4 cytopenias including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Monitor blood counts as medically appropriate (seeTable 24 of the Investigator's Brochure).

Subjects with cytopenias should be managed according to institutional guidelines with maximalsupportive care and diagnostic evaluations as clinically indicated. Subjects should be closely monitored as appropriate.

1.4.2.4 *Second Primary Malignancies*

Events of second primary malignancies, including non-skin carcinomas, have occurred in clinical studies with acalabrutinib. The most frequently reported second primary malignancy was skin cancer (see Table 24 of the Investigator's Brochure).

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 medical monitor.

1.4.2.5 *Atrial Fibrillation*

Events of atrial fibrillation/flutter have occurred in clinical studies with acalabrutinib, particularly in subjects with cardiac risk factors, hypertension, diabetes mellitus, acute infections, or a previous history of atrial fibrillation (see Table 24 of the Investigator's Brochure).

Monitor for symptoms of atrial fibrillation and atrial flutter (e.g., palpitations, dizziness, syncope, chest pain, dyspnea) and obtain an ECG as clinically indicated. Subjects with atrial fibrillation should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.

1.5 R-ICE

R-ICE is one of the most common implemented salvage chemotherapy for r/r DLBCL with CR rate of 63.5%. Hematologic toxicity is universal with 57% of patients requiring transfusion of blood products. Grade 3 and 4 toxicities include neutropenic fever and infections. Subjects should be closely monitored for infection and need for blood products. As describe on section 3.6 all subjects included in the study will require G-CSF on day 5 after chemotherapy.

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2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE:

The primary objective is to improve CR rate of R-ICE for rel/ref non-GC DLBCL from 29% to 50% with acalabrutinib + R-ICE for 3 cycles by RECIL.[1]

2.2 SECONDARY OBJECTIVE(S):

- Safety and tolerability of acalabrutinib with R-ICE in patients with rel/ref DLBCL
- PR, CR, ORR of acalabrutinib + R-ICE
- Ability to mobilize > 2 x10^6 CD34+ cells/kg
- EFS, PFS and OS at 1 year

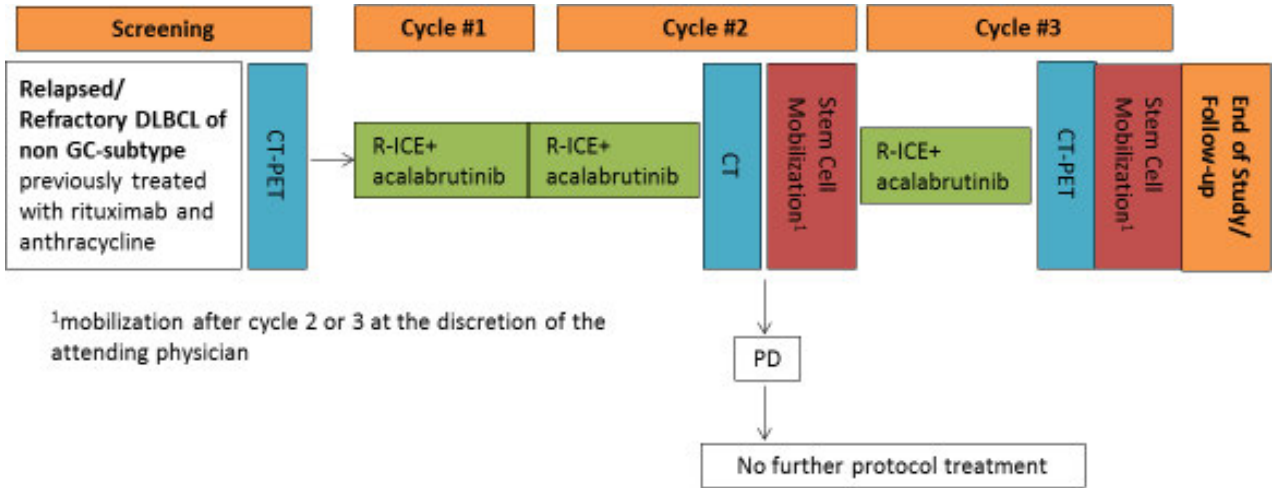
2.3 EXPLORATORY OBJECTIVE(S)

Correlate efficacy endpoints (ORR, PFS, OS) with: baseline metabolic tumor volume (MTV), circulating cell-free tumor DNA (ctDNA), and the results of next-generation sequencing (NGS) of tumor. NGS in diagnostic biopsy if available.

3 STUDY DESIGN

This is a multi-center, open-label, single arm phase II study of acalabrutinib in combination with R-ICE in rel/ref non-GC DLBCL per Hans criteria,[2] transformed CLL/SLL (tCLL/SLL) and transformed marginal zone lymphoma (MZL). Please see schema below.
The study schema is provided below (Figure 3-1).

Figure 3-1. Study Schema



3.1 STUDY PARAMETERS

3.1.1 Efficacy Parameters

EFS, PFS, OS

PFS is defined as the time from start of study entry until disease progression or death. EFS is measured from the time from study entry to the event. Events are defined by: progression of disease, death, or removal from study for any reason. OS is defined as the time from study entry or initial diagnosis until death from any cause.

3.1.2 Safety Parameters

The safety of acalabrutinib in combination with R-ICE will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent AEs or abnormalities of laboratory tests; SAEs; DLTs, or AEs leading to discontinuation of study treatment or death.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting.
(see Section 6).

3.1.3 Pharmacodynamic, Pharmacokinetic and Biomarker Parameters

Exploratory correlative studies of tumor tissue, when available, may include characterization of tumor subtypes by NGS, including comparing pre- and post- study treatment biopsies in patients without a clinical response and/or progression of disease. Baseline and end of treatment (EOT) PET scan will be assessed for response by MTV as a correlative biomarker.

3.2 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

As described in Section 1.4, acalabrutinib is currently being evaluated in a Phase 1/2 study in subjects with CLL, Richter's syndrome, or prolymphocytic leukemia (ACE-CL-001). In this study, subjects have received oral dosages of 100 to 400 mg QD and 100 to 200 mg BID of acalabrutinib. All tested dose levels have been well tolerated. No DLT has occurred at any dose level and the MTD was not reached. PD results from this study also show 100 and 200 mg BID have the highest Btk occupancy at 24 hours of all the regimens evaluated. Robust clinical responses have been observed (Investigator Brochure 9.0 section 5.2.3.1).

The dosing of R-ICE has been extensively studied including in phase I with the BTK inhibitor ibrutinib.[21]

3.3 SELECTION OF STUDY POPULATION

3.3.1 Inclusion Criteria

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria:

1. Men and women ≥ 18 years of age.
2. Patients must have histologic confirmation of relapsed or refractory lymphoma.
3. Baseline FDG-PET scans must demonstrate positive lesions compatible with CT defined anatomical tumor sites.
    a) CT scan showing at least:
        i) 2 or more clearly demarcated lesions/nodes with a long axis >1.5cm and short axis ≥1.0cm, or
        ii) 1 clearly demarcated lesion/node with a long axis >2.0cm and short axis ≥1.0cm.
4. Patient must have been previously treated for B cell non-Hodgkin lymphoma with any of the allowable below:
    a) First-line treatment with rituximab and an anthracycline-based chemotherapy.
    b) Monotherapy rituximab, dosed prior to first-line rituximab combined with anthracycline containing chemotherapy, or as maintenance therapy.
    c) Radiotherapy as part of the first-line treatment plan including anthracycline and rituximab.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (See Appendix 2)
6. Life expectancy of greater than 6 weeks.
7. Patients must have normal organ and marrow function as defined below,
    a) absolute neutrophil count ≥1000/mcL (unless due to lymphoma involvement of the bone marrow)
    b) platelets ≥75,000/mcL (unless due to lymphoma involvement of the bone marrow)
    c) total bilirubin <1.5 x within normal institutional limits (unless due to lymphoma involvement of liver or a known history of Gilbert's disease)
    d) AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal (unless due to lymphoma involvement of liver)
    e) creatinine within normal institutional limits, or
    f) creatinine clearance ≥40 mL/min/1.73 m2 for patients with creatinine levels above institutional normal. (unless due to lymphoma)
8. Major surgical procedure within 28 days of first dose of study drug. 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.
9. Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of acalabrutinib + R-ICE.
10. Men who are sexually active and can beget children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of acalabrutinib + R-ICE.
11. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of study drug.
12. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
13. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations).

3.3.2 Exclusion Criteria

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1. Germinal-center cell-of-origin DLBCL[22]

2. Patients who have had chemotherapy or radiotherapy < 21 days prior to first administration of study treatment or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.
3. Patients who are receiving any other investigational agents.
4. Patients with known central nervous system involvement of lymphoma.
5. History of allergic reactions attributed to compounds of similar chemical or biologic composition to acalabrutinib or R-ICE with the exception of first-infusion reaction to rituximab.
6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. Recent infections requiring systemic treatment need to have completed therapy > 7 days before the first dose of study drug.
7. Pregnant women are excluded from this study because an acalabrutinib R-ICE is a chemotherapy program with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with acalabrutinib R-ICE, breastfeeding should be discontinued if the mother is treated with acalabrutinib R-ICE.
8. HIV-positive patients on combination antiretroviral therapy are eligible, unless the patient's CD4 count is below the institutional lower limit of normal, or the patient is taking prohibited CYP3A4/5 strong inhibitors or inducers.
9. Patients may not have received any anti-cancer therapy for their primary rel/ref DLBCL with the exception of palliative RT.
10. Uncontrolled Autoimmune Hemolytic Anemia or ITP resulting in (or as evidenced by) declining platelet or Hgb levels within the 4 weeks prior to first dose of study drug.
11. Presence of transfusion-dependent thrombocytopenia.
12. Prior exposure to a BTK inhibitor.
13. History of prior malignancy, with the exception of the following:
    a) Malignancy treated with curative intent felt to be at low risk for recurrence by treating physician
    b) Adequately treated non-melanomatous skin cancer or lentigo maligna melanoma without current evidence of disease
    c) Adequately treated cervical carcinoma in situ without current evidence of disease.
14. Currently active clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification, or history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to first dose with study drug.
15. Unable to swallow capsules, or disease significantly affecting gastrointestinal function or, resection of the stomach or small bowel, or symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
16. Serologic status reflecting active hepatitis B or C infection. Patients that are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody will need a negative polymerase chain reaction (PCR) prior to enrollment. (PCR positive patients will be excluded.) Hepatitis C antibody positive patients are eligible if PCR is negative. Hepatitis B core antibody (+) patients without evidence of HBsAg or Hep B PCR (+) are eligible with appropriate Hepatitis B reactivation prophylaxis.
17. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
18. Current life-threatening illness, medical condition, or organ system dysfunction which, in the Investigator's opinion, could compromise the patient's safety, or put the study at risk.
19. Received anticoagulation therapy with Coumadin or equivalent vitamin K antagonists within the last 28 days.
20. Vaccinated with live, attenuated vaccines with 4 weeks of first does of study drug.

21. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 5), grade ≤1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.
22. Known bleeding disorders (e.g., von Willebrand's disease) or hemophilia.
23. Unwilling or unable to participate in all required study evaluations and procedures.
24. Currently active, clinically significant hepatic impairment (≥ moderate hepatic impairment according to the NCI/Child Pugh classification.
25. Breastfeeding or pregnant.
26. Concurrent participation in another therapeutic clinical trial.
27. Patients who require proton pump inhibitors at baseline (prior to fist dose of study drug) or strong CYP3A4 inhibitor or inducer and are not able to switch to another medication

3.3.3 Recruitment

Investigators and designated personnel from the research study team at University of Miami Sylvester Comprehensive Cancer Center (SCCC) and if applicable other sites (for multi-center studies) will identify, recruit, enroll and treat eligible patients for the study. This study will access electronic medical record or other protected health information without obtaining a signed HIPAA authorization from the subject to identify potential subjects for recruitment and to obtain study data. At the University of Miami SCCC, subjects will be recruited via clinical practice offices. Additional study sites will recruit subjects as per institutional guidelines.

3.4 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

3.4.1 Discontinuation of Study Intervention

Discontinuation from protocol treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the Investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the data collected during the safety evaluation visit and follow-up information.

3.4.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An Investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive investigational treatment for 21 days/weeks.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

3.4.3 Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials

An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). In accordance with FDA regulations, IRB approval of informed consent documents would be required (21 CFR 50.25, 56.109(b), 312.60, 312.66, 812.100).

3.4.4 Participant Replacement Criteria

Subjects who sign the informed consent form and are enrolled but do not receive the investigational treatment may be replaced. Subjects who sign the informed consent form, receive the protocol treatment, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

3.4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. Screen failures will be rescreened if they are eligible at a later time.

3.4.6 Lost to follow up

A participant will be considered lost to follow-up if he or she fails to return for three scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- **For Missed Treatment Visits:** The site will attempt to contact the participant and reschedule the missed treatment visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- **For Missed Post-Treatment Follow-Up Visits:** The site will attempt to contact the participant and reschedule the missed post-treatment follow visit within $\leq$14 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

3.5 STUDY DRUG

3.5.1 Premedications

R-ICE will be administered per standard institutional procedures with appropriate hydration and premedication per institutional standards.

3.5.2 Formulation, Packaging, and Storage

Acalabrutinib

The investigational product, acalabrutinib capsules for oral administration, is supplied as yellow and blue, opaque hard gelatin capsules, with 100 mg of acalabrutinib as the active ingredient. The capsules will be supplied by the supplier of the study medication and provided to participants at no cost. Each capsule also contains compendial inactive ingredients: silicified microcrystalline cellulose, which is composed of microcrystalline cellulose and colloidal silicon dioxide, partially pregelatinized starch, sodium starch glycolate, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide and indigotine (FD&C Blue 2).

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

Refer to the acalabrutinib Investigator Brochure for additional information regarding the drug product to be used in this trial.

3.5.3 Administration of Study Drug

Acalabrutinib capsule is to be taken orally approximately every 12 hours.

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.

Guidance on co-administration of acalabrutinib with agents that affect gastric pH is provided in Section 3.10.2.

R-ICE will be administered as per standard institutional policy.

3.5.4 Assuring Subject Compliance

For treatments that are taken in the clinic, subjects should take the dose from the drug dispensed for them for that particular time period. All other acalabrutinib treatments will be taken at home. Subjects will receive a medication diary to record the specific time each dose was taken and to record reasons for any missed doses (Appendix 6).

Subject compliance with acalabrutinib dosing will be assessed at every clinic visit. The subject will be instructed to bring the diary and any remaining capsules to the clinic at their next visit. The study staff will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded as described in Section 7.6. Returned capsules must not be redispensed to another subject.

3.6 STUDY TREATMENT SCHEDULE

This is a phase II study of acalabrutinib in combination with R-ICE for rel/ref DLBCL non-GC-subtype.

R-ICE will be administered as per standard institutional policy.

3.7 DURATION OF THERAPY

In the absence of treatment delays due to adverse event(s), treatment may continue for 3 cycles or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Patients that achieve a partial or complete remission following 3 cycles of therapy, per criteria outlined in Section 4.1.16, and have mobilized $\geq$ 2 x 10^6 CD34+/kg, will be eligible to proceed to autologous transplantation at the discretion of the treating physician. Patients will have completed study following 3 cycles of therapy and will be subject to follow-up per Section 4.2 and 4.3.

3.8 DOSING DELAYS AND MODIFICATIONS

Treatment modifications

Treatment-emergent adverse events of R-ICE therapy predominantly comprise of hemato-toxicities (such as neutropenia, leukopenia, thrombocytopenia, and anemia). Nonhematologic disorders include asthenia, sensory disturbance, mucositis, alopecia, sepsis, dyspnea, back pain, hyperglycemia, hypersensitivity, and cardiac disorders. Tumor lysis syndrome will be managed as per institutional guidelines. Renal and hepatic adverse reactions will be managed as per institutional guidelines. Treatment modifications are not permitted for R-ICE.

Cycle delay

After completion of each 21-day cycle, the start of a new cycle could be delayed for up to one 1 week (7 days) in cases of toxicity necessitating a dose delay. A subject whose cycle is delayed should be assessed within a week for resolution or recovery of toxicity and a decision regarding further delay. There is no limit on the number of cycle delays that each subject may experience, as long as delays do not exceed one week or 28 days from the beginning of a cycle.

The following parameters must be met on the first day of a new cycle (after cycle 1):

- Platelet count $\geq$ 50 x 10^9/L
- ANC $\geq$ 1.0 x 10^9/L
- Non-hematologic toxicity of ≥ grade 3 must have recovered to baseline or Grade ≤ 1

For severe hematologic toxicity (grade $\geq$ 3), laboratory evaluations may be repeated more frequently as necessary until the retreatment requirements are met. In the event of severe renal toxicity or hepatotoxicity, laboratory tests may be repeated more frequently as necessary until the toxicity resolves.

Dose modifications and dose limiting toxicities (DLT) acalabrutinib + RICE

Given that acalabrutinib has not been studied in phase I combination with R-ICE, a 3-6 patient lead-in will be conducted at the acalabrutinib 100 mg PO BID dosing. If one DLTs is observed within the first 3 patients, or if two DLTs are observed within the first 6 patients, a dose level (-)1 of acalabrutinib at 100 mg PO daily will be instituted for the next 3-6 patients. If > 2 DLTs are observed within the next 6 patients, the study will be terminated.

Dose Limiting Toxicity: acalabrutinib + R-ICE

The DLT evaluation period begins with the first dose of acalabrutinib and ends immediately prior to the initiation of the second cycle. Only toxicities that occur during the DLT period will be used for the purposes of defining DLT. However, toxicities that occur in all cycles will be considered in the overall decisions of the investigators. The first 3-6 subjects will be evaluated for DLTs per above. Subjects considered non-evaluable for DLT may be replaced, but the safety profile of these subjects will be included in the investigator review. Subjects considered non-evaluable for DLT are subjects who do not complete Cycle 1 for reasons other than toxicity. Subjects who experience a DLT may continue treatment on the study at a lower dose of acalabrutinib.

The following will be considered DLTs after confirmation by the investigators:

- Complete treatment interruption of more than 7 days (28 days of the cycle) for acalabrutinib-RICE-related Grade ≥ 2 toxicities within Cycle 1

- Any Grade 3 or Grade 4 non-hematological toxicity that is at least possibly related to the study drugs
  - excluding:
    - Grade 3 nausea or vomiting responsive to anti-emetic treatment,
    - Grade 3 diarrhea responding to anti-diarrheal treatment,
    - Grade 3 fatigue/asthenia unless persisting for 7 days after stopping acalabrutinib and absent at baseline
    - alopecia
  - including:
    - persistent Grade ≥ 2 nausea and/or vomiting despite prolonged (more than 7 days continuously) anti-emetic treatment (5 HT3 antagonist, antihistamine, metoclopramide)
- Grade ≥ 2 hemorrhagic events requiring medical intervention
- Grade 4 hematological toxicity defined as:
  - Febrile neutropenia (ANC < 500 cells/μL with fever [body temperature ≥ 38.5°C] or sepsis) or Grade 4 neutropenia (ANC < 500 cells/μL) requiring at least 1 week delay of the next treatment cycle
  - Grade 4 thrombocytopenia (Platelet count < 25,000 cells/μL) requiring at least 1 week delay of next treatment cycle

Based on the specific adverse event observed, 1 dose level reduction is permitted for acalabrutinib (see Table below). If acalabrutinib is withheld for ≤ 1 week due to acalabrutinib-related toxicity; study drug should be resumed with a dose reduction when treatment resumes following recovery from the toxicity. If there is unacceptable toxicity despite 1 dose reduction the treatment should be discontinued. If treatment must be withheld for an acalabrutinib-related adverse event that fails to resolve to an acceptable level (eg, ≤ Grade 1 nonhematologic toxicity) within 1 week after the date acalabrutinib was withheld, treatment with acalabrutinib should be permanently discontinued. In this event, the subject will be discontinued from the treatment, and End-of-Treatment Visit assessments will be performed including through the protocol-specified AE reporting window and have follow-up for ongoing SAEs to resolution or stability unless the subject lost to follow-up. (see section 6.2.6)
Acalabrutinib dose adjustments also apply to cycle 1.
Acalabrutinib dose will not be reduced for hematological toxicities unless the hematologic toxicities fail to recover by day 21 of a cycle.

The actions in the table below should be taken for the following toxicities at day 21 of the cycle:

- Grade 4 ANC (<500/μL) for >7 days
- Grade 3 thrombocytopenia (<50,000/mcL) in the presence of clinically significant bleeding events
- Grade 4 thrombocytopenia (<25,000/mcL)
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent, despite optimal antiemetic and/or anti-diarrheal therapy
- Any other Grade 4 or unmanageable Grade 3 toxicity.

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of acalabrutinib treatment*. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation.*

Dose Reduction Schedule for Acalabrutinib

Starting dose (mg/day)	Dose reduction 1 (mg/day)
200 (100 mg BID)	100 (100 mg QD)

Dose reductions below 100 mg/day are not permitted.

Non-hematological grade 3 or higher toxicities

- For Grade 3 possible or probable acalabrutinib-related non-hematologic toxicities (other than the adverse events specifically described in this section), therapy (acalabrutinib and R-ICE) is to be held for a maximum of 1 week (and d28 of a cycle) until the toxicity returns to Grade 1 or less. If grade 2 during the first cycle, this will be considered a DLT.
- For any Grade 4 non-hematologic toxicity attributed to acalabrutinib, discontinue acalabrutinib and chemotherapy for all remaining cycles; subject is discontinued from study treatment and must complete protocol-specified AE reporting along with follow-up for ongoing SAEs to resolution unless the subject is lost to follow-up.
- If Grade 3 toxicity returns to Grade 1 or less by Day 28, then proceed with next cycle of therapy with acalabrutinib reduced to the next lower dose level.

Overdose

Any dose of study drug administered in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate time frame (see Section 6.2.2) and documented as clinical sequelae to an overdose.

There is no specific experience in the management of acalabrutinib overdose in patients.

Dose Modification for Hepatic Impaired Subjects (Child-Pugh Criteria)

Acalabrutinib is metabolized in the liver. Please see the Child-Pugh scoring system outlined in Appendix G to determine whether dose modifications are warranted according to the following instructions. For patients who develop mild-moderate liver impairment while on study (Child-Pugh class A), the recommended dose is acalabrutinib 100 mg daily. Patients who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better and may be re-treated according to resolved hepatic conditions. Monitor patients for signs of toxicity and follow dose modification guidance as needed.

3.9 CONCOMITANT THERAPY

3.9.1 Permitted Concomitant Therapy

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines.[23] Transfusions may be given in accordance with institutional policy.

Short courses (≤14 days) of steroid treatment that do not exceed 100 mg per day of prednisone or equivalent are permitted.

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

The following may be considered: localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

3.9.2 Prohibited or Restricted Concomitant Therapy

Any non-study related chemotherapy, anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone >100 mg/day for longer than 2 weeks), experimental therapy, or radiotherapy for treating DLBCL are prohibited.
Warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) are prohibited.
For additional information on drugs with potential drug-drug interactions, refer to Section 3.10.2.

3.9.2.1 CYP Inhibiting/Inducing Drugs

Based on available nonclinical and clinical data, acalabrutinib is almost completely metabolized by multiple CYP and non CYP metabolic pathways. CYP3A-mediated oxidation is the major route of metabolism in humans. Additional studies were performed in a human liver microsomal system with specific chemical inhibitors of individual CYP isoforms. Inhibition of acalabrutinib metabolism by specific CYP3A4/5 inhibitors (ketoconazole and troleandomycin) indicate that CYP3A4/5 is the predominant CYP isoform responsible for metabolism of acalabrutinib.

PBPK modeling predicted the magnitude of changes in acalabrutinib and active metabolite exposure due to a variety of moderate CYP3A inducers and inhibitors. Avoid coadministration of strong CYP3A inhibitors (such as itraconazole and rifampin) with acalabrutinib on study, if possible. If moderate or strong CYP3A inhibitors are required on study, monitor subjects for toxicity (refer to IB section 6.7). A list of common CYP3A4/5 inhibitors or inducers is provided at http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

- If acalabrutinib must be administered with a strong or moderate CYP3A4/5 inhibitor, the Medical Monitor should be consulted before use, and a dose reduction of acalabrutinib to 100 mg PO daily or temporarily holding acalabrutinib should be considered. Patients should be closely monitored for potential treatment-related toxicities.

- There was minimal involvement of CYP1A2, CYP2E1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 in the metabolism of acalabrutinib in human liver microsomes.. Therefore drugs that are known to be CYP1A2, CYP2E1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 inhibitors or inducers are not restricted.

3.9.2.2 QT Prolonging Agents

Therapeutic plasma acalabrutinib concentrations after a 100-mg dose or supratherapeutic plasma acalabrutinib concentrations after a 400-mg dose in healthy subjects did not prolong the QTc interval in a thorough QT study.
Medications known to cause Torsades des Pointes should be avoided. Refer to the Arizona CERT website (http://www.azcert.org/medical-pros/drug-lists/list-01.cfm?sort=Generic_name) or similar websites for a list of these medications. If no alternative treatment is available, the Medical Monitor must be consulted.
Any medications known to cause QT prolongation may be used with caution; periodic monitoring with electrocardiograms (ECGs) and electrolytes should be considered.

3.9.2.3 Drugs That May Have Their Plasma Concentration Altered by Acalabrutinib

Acalabrutinib is a substrate for breast cancer-related protein (BCRP). Acalabrutinib coadministration may increase exposure to BCRP substrates by inhibition of intestinal BCRP. Use caution with coadministered, oral, narrow therapeutic index BCRP substrates.

3.9.2.4 Antiplatelet Agents and Anticoagulants

Patients receiving antiplatelet or anticoagulant therapies in conjunction with acalabrutinib may be at increased risk of hemorrhage and should be monitored for signs of bleeding, as described in section 1.4.2.1.

3.9.2.5 Surgery

Patients who require surgery for any reason while on study are recommended to withhold acalabrutinib for 3-7 days pre- and post-surgery, depending upon the type or surgery and the

risk of bleeding. Patients must have recovered adequately from any toxicity and/or complications from the intervention before the first dose or before restarting acalabrutinib.

3.10 PRECAUTIONS

3.10.1 Dietary Restrictions

Acalabrutinib can be taken with or without food. There are no dietary restrictions for R-ICE.

3.10.2 Drug-drug Interactions & Infusion Reactions

Acalabrutinib is metabolized by CYP3A. At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated.

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 3) 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.

Infusion reactions related to rituximab, etoposide, ifosfamide, or carboplatin should be managed according to the package insert and/or institutional standard of care.

3.10.3 Contraception Requirements

Contraception Requirements for Women:

The following are acceptable measures to avoid becoming pregnant:

- Abstinence (not having sexual relations with a person of the opposite sex)
- Implantable hormone (e.g. Norplant)
- Intrauterine Device (IUD)
- Male partner has had a vasectomy
- Female sterilization
- Hormonal injection
- Oral contraceptives
- GnRH Agonists (zoladex, triptorelin, leuprolide)-these agents are only effective if they have been in continuous use for at least 3 months

Participants must use contraception, at least starting at screening, before starting study treatment unless they abstain from sexual intercourse. Participants must use contraception during study treatment and for at least 90 days after stopping study treatment.

Female participants should not become pregnant, breastfeed, or donate an egg for at least 90 days after the last dose of study medication. If female participants become pregnant while participating in the study or within 1 year of completing study treatment, they should inform their study doctor immediately.

Contraception Requirements for Men:
One of the following forms of contraception should be used by men or their female partner of childbearing potential:

- Abstinence (not having sexual relations with a person of the opposite sex)
- Implantable hormone (e.g. Norplant)
- Intrauterine Device (IUD)
- Vasectomy
- Female sterilization
- Hormonal injection
- Oral contraceptives

Male participants must use contraception during study treatment and for at least 90 days after stopping study treatment. Participants should also refrain from donating semen during therapy and for at least 1 year after stopping the therapy.

There is theoretical concern that study treatment can result in sperm abnormalities and/or can transmit harmful substances in their semen during sex. Therefore, males must remain abstinent or use a condom, even if they have undergone a vasectomy.

If a female partner becomes pregnant or suspects becoming pregnant during study treatment or within 1 year after completing study treatment, the Study Doctor must be informed immediately. The study Doctor may want to follow the pregnancy and may ask the female partner to sign a consent form so they can collect information about the outcome of the pregnancy.

3.10.4 Overdose Instructions

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.
All AEs associated with an overdose or incorrect administration of study drug should be recorded on the CRF and reported to Acerta/AZ per contractual guidelines (See Section 6.2.1 for Adverse Event Reporting Period).
In the event of subject ingestion of more than the recommended acalabrutinib dosage, observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion of acalabrutinib is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

3.11 WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

The investigator may withdraw any subject from study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.
Any subject has the right to withdraw from the study at any time. In addition, subjects may be withdrawn from study treatment for the following reasons:

- Study treatment should be discontinued in the event of a toxicity lasting > 28 days as described in Section 3.8.
- Any subject who has **confirmed** objective evidence of cancer progression while receiving study treatment should be withdrawn from the study treatment. If there is uncertainty regarding whether there is true cancer progression, the subject may continue study treatment and remain under close observation (eg, evaluated at 4-week intervals) pending confirmation of progression.
- Any subject whose medical condition substantially changes after entering the study should be carefully evaluated by the investigator. Such subjects should be withdrawn from study treatment if continuing would place them at risk.
- Any subject who becomes pregnant or begins breastfeeding should be removed from study treatment.
- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn from study treatment in circumstances that increase risk or substantially compromise the interpretation of study results.

3.12 REMOVAL FROM STUDY

Reasons for removal of a subject from the study are:

- Subject's withdrawal of consent from study
- Decision by sponsor to terminate the study
- Subject lost to follow-up
- Death

3.13 DATA AND SAFETY MONITORING

The Sylvester Comprehensive Cancer Center (SCCC) Data and Safety Monitoring Committee (DSMC) will monitor this clinical trial according to the Cancer Center's Data and Safety Monitoring Plan (DSMP). In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study.

DSMC oversight of the conduct of this trial includes ongoing review of accrual and adverse event (AE) data, and periodic review of the study therapy. The guidelines appearing in the Section 3.8 are offered for DSMC consideration in assessing AEs and pathologic objective response. In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action. The SCCC DSM Plan to which this study is subject can also be found at **WWW.SYLVESTER.ORG**.

3.14 STUDY AUDITING AND MONITORING

This study will be monitored (as applicable) and may be audited according to the University of Miami requirements. See also
http://research.med.miami.edu/clinical-research/crors/monitoring

Following the monitoring plan, the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

3.14.1 Trial Monitoring, Auditing, and Inspecting

The investigator will permit trial-related monitoring, quality audits, and inspections by, government regulatory authorities, of all trial-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable trial-related facilities. The investigator will ensure that the trial monitor or any

other compliance or QA reviewer is given access to all trial-related documents and trial-related facilities.

Participation as an investigator in this trial implies the acceptance of potential inspection by government regulatory authorities.

3.15 QUALITY ASSURANCE AND QUALITY CONTROL

In addition to the Clinical Monitoring component of this protocol, Quality Assurance (QA) will be implemented to assess compliance with GCP and applicable regulatory requirements. Data or documentation audited shall be assessed for compliance to the protocol, accuracy in relation to source documents and compliance to applicable regulations.

4 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 1.

Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.5.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated.

4.1 DESCRIPTION OF PROCEDURES

4.1.1 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate). For subjects not qualified or able to give legal consent, consent must be obtained from a parent, legal guardian, or custodian. The investigator or designee must explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

4.1.2 Medical History

Collect and record the subject's complete history through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, and responses and duration of response to these treatments, also will be recorded.

4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1. All medical occurrences from the time of first dose that meet this definition must be recorded. Important additional requirements for reporting SAEs are explained in Section 6.2.

4.1.4 Concomitant Medications and Therapy

All concomitant medications and procedures from within 21 days before the start of study drug administration through 30 days after the last dose of study drug must be documented.

4.1.5 Confirmation of Eligibility
Subject eligibility for enrollment will be assessed per Section 3.3. All screening procedures, unless otherwise indicated, should be completed within 28 days of the first dose of study drug.

4.1.6 ECOG Performance Status
The ECOG performance index is provided in Appendix 2.

4.1.7 Physical Examination, Height & Weight, & Vital Signs
The physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system with lymphoma symptoms reviewed and recorded.
Vital signs (blood pressure, heart rate, and body temperature) will be assessed after the subject has rested in the sitting position.
Directed physical exam will be performed every day while participant is receiving R-ICE treatment.

4.1.8 Electrocardiogram
Subjects should be in supine position and resting for at least 10 minutes before any study-related ECGs.

4.1.9 Urine or Serum Pregnancy Test
Pregnancy tests will be required only for women of childbearing potential. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.10 Hematology
Hematology studies must include complete blood count (CBC) with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC). Testing will be done by a local laboratory as listed on the investigator's Form FDA 1572.

4.1.11 Serum Chemistry
Chemistry will include albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.
If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Testing will be done by a local laboratory as listed on the investigator's Form FDA 1572.
Chemistry (potassium) will be performed every day while the participant is receiving R-ICE treatment.

4.1.12 Urinalysis
Urinalysis will be performed every day while the participant is receiving R-ICE treatment.

4.1.13 Hepatitis B and C Testing
Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), and HCV antibody. In addition, any subjects testing positive for any hepatitis serology must have PCR testing during screening and on study (see exclusion criterion #15).

4.1.14 Coagulation Panel
Coagulation panel will include prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR). Testing will be done by a local laboratory as listed on the investigator's Form FDA 1572.

4.1.15 Pharmacodynamics/Pharmacokinetics and Biomarker Studies
TUMOR BIOPSY and ctDNA:
Identification of Tumor-Specific BCR Clonotype from pre-treatment tumor biopsy and tracking of MRD:
The specimens collected at pre-treatment (typically, lymph node biopsy) archival tissue will be shipped to Foundation One Heme. Details regarding recommended specimens are outlined in the Manual of Procedures

ctDNA CORRELATES

Pre-treatment blood samples can be used as an adjunct specimen to identify DLBCL specific B cell receptor (BCR) clonotypes. Briefly, 400 ng of total RNA isolated from buffy coat will be used to prepare BCR IGH plus IGL (κ+γ) sequencing libraries using ArcherDx Immunoverse BCR All Chains panel. Libraries will be sequenced on an Illumina MiSeq to a depth of 1M read-pairs (2x300bp) per sample, sufficient to identify dominant clones using a frequency threshold of 5%. Archer Analysis pipeline will be used for preprocessing (sample demultiplexing, alignment and molecular index counting for bias correction) and BCR repertoire analysis to identify major BCR clones (clone, clonotype, and segment usage analysis). MRD assessment using BCR repertoire analysis of peripheral blood buffy coat will follow an identical workflow but using 1,600 ng of input RNA and sequencing to a depth of 4M read-pairs per sample to permit tracking of low frequency BCR clones. The DLBCL derived BCR clones identified in each pre-treatment sample will be used to assess the presence of MRD in post-treatment samples with a sampling limit of of >75,000 clonotypes per assay. MRD determined in this manner, as DLBCL-derived BCR clone counts within the B cell compartment, will be normalized to total cells or standard blood volume using single platform clinical flow cytometry (Laboratory of Flowcytometry, Department of Pathology and Laboratory Medicine, University of Miami). The BCR immune repertoire approach will also permit screening of the expansion of novel high frequency BCR clones should they emerge.

Response Criteria: Response will be evaluated in this study using the RECIL criteria and will be applied to define complete response. Response will be evaluated first at pre-treatment, and subsequently at interim CT after two cycles of therapy, and at EOT PET. We will follow patients who achieve a complete metabolic response after completion of study therapy during surveillance for 52 weeks with CT or PET/CT per standard of care until progression of disease by imaging.

As an exploratory objective we will collect circulating cell free DNA (ccfDNA) at each assessment to support analysis of circulating tumor DNA (ctDNA). ctDNA analysis will require the targeted sequencing of known mutant alleles which may not be apparent for all cases. In cases where genomic alterations in the DNA components of the FoundationOne Heme panel are identified pre-treatment, orthologous ctDNA-optimized assays using either commercial or custom targeted sequencing panels will be used to retrospectively track ctDNA variant allele frequencies. In addition, these ccfDNA samples could also be used for comparative retrospective analysis of BCR clonotypes if assays become available.
Refer to the laboratory manual for instructions on collection and shipment of the PD and biomarker samples. All testing will be done by the supplier of the study medication or designee. Leftover blood and tumor samples may also be used for genomic analyses to study mechanisms of action.

MTV CORRELATE:

Screening and EOT scans for each patient enrolled will be sent to UM for central review.

PET/CT scans at enrollment and EOT from mid-skull to upper thighs will be obtained ~90 minutes after injection on Philips Gemini TF PET/CT systems (Philips Medical Systems, Cleveland, Ohio). A clinical imaging protocol will be applied with an injection of approximately 555 +/- 10% MBq FDG after at least 4 hours of fasting and documentation of blood glucose <200 mg/dL. A low-dose, attenuation correction CT scan (120 kV, approximately 100 mA) will be acquired, following by PET emission images. All images will be reviewed on Thinking Systems software. Region of interest will be set by manual adjustment in 3 planes to exclude adjacent physiologic FDG avid structures. SUV max will be defined as the maximum voxel intensity within the volumetric region of interest. A threshold of 41% of the maximum signal intensity will be used to delineate the metabolic tumor volume (MTV) however, other thresholds will be evaluated. Patient MTV represents the sum of every individual lesion MTV. The TLG will be calculated as the product of MTV and the SUV mean using Hermes Hybrid 3D Tumor Finder for MTV software.

4.1.16 Tumor Assessments

Response will be evaluated in this study per RECIL criteria.[1]

Complete Response (CR):

- CR is defined as a complete resolution of all target lesions by CT scans with complete normalization of FDG-PET uptake in all areas (Deauville score of 1–3), and bone marrow biopsy negativity (if it was positive or unknown at baseline). If pretreatment PET scan was negative, lymph nodes that measured ≥15 mm in the long axis should regress to < 10 mm.
- CR is also defined as achievement of a partial remission by CT scan criteria (reduction in sum of longest diameters by CT imaging by >30%) with normalization (Deauville score 1–3) of FDG-PET activity in FDG-avid lymphoma (Table 1). Because many novel targeted agents may alter glucose uptake and/or metabolism, normalizing of FDG-PET imaging alone is not sufficient by itself to determine CR status unless accompanied with a significant (>30%) decrease in the sum of diameters. Accordingly, a reduction in the sum of diameters by ≤30% with normalization of FDG-PET uptake should not be considered a CR unless documented by a negative tissue biopsy.
- Deauville Criteria 5-point scale[32]:
    1. No uptake.
    2. Uptake ≤ mediastinum.
    3. Uptake > mediastinum but ≤ liver.
    4. Uptake moderately more than liver uptake, at any site.
    5. Markedly increased uptake at any site and new sites of disease.
- In cases where pretreatment baseline tumor burden is low, with only a few lesions measuring around 2 cm in longest diameter, treatment effect may shrink the long axis of a target lymph node to a normal values of <10 mm.

Partial Response (PR):

- PR is defined as a reduction of the sum of longest diameters of target lesions by ≥30%, but without meeting the definition of CR. If one or more target lesions grew in size but the sum of the diameters remains ≤30% of the baseline measurement, and no new lesions appear, the response should be designated PR.

Minor Response (MR):

- Using single diameter long-axis measurements, MR is defined as a reduction in the SLD of target lesions by ≥10% but <30%, without the appearance of any new lesions, and irrespective of PET scan results.

Stable Disease (SD):

- SD is defined as changes in the SLD of targeted lesions ranging between reduction of <10% to an increase by ≤20% without the appearance of a new lesion, and irrespective of PET results.

Progressive Disease (PD):

- PD is defined as an increase in the sum of longest diameters of target lesions by >20%, and/or appearance of a new lesion (lymph node ≥ or a soft tissue mass ≥10 mm of the longest diameter), irrespective of FDG-PET results. An increase in the size of previously involved small lymph nodes by >20% while other lesions are decreasing, especially at the beginning of treatment with investigational agents, may represent a tumor flare and should not be designated a PD, unless there is continued increase in size on

subsequent imaging studies.

- **Response assessment in patients receiving agents that mobilize lymphoma cells from lymph nodes and bone marrow into the blood**
    - Some agents can inhibit adhesion mechanisms in tumor cells causing redistribution of tumor cells from lymph nodes and/or bone marrow into the blood. Thus, while lymph node size decrease in response to therapy, the tumor cell count increases in the blood, creating another form of "pseudo-progression". With continued therapy, blood lymphocytosis decrease as tumor cells start to die. Increased lymphocytosis in the setting of a decrease in lymph node measurement is not considered PD, and response designation should depend on lymph nodes and extra-nodal disease measurement. Lymphocytosis can be included as annotation. For example, PR with increased lymphocytosis.

4.1.17 Study Drug Accountability

See Section 7.6

4.2 ASSESSMENT OF RESPONSE TO TREATMENT

For the purposes of this study, patients should be re-evaluated per the study calendar. In addition to a baseline scan, confirmatory scans will also be obtained post cycle 2 per cross sectional imaging criteria by CT,' as well as post cycle 3 per RECIL criteria[1] following initial documentation of an objective response following cycle 2. If patients have progressive disease after cycle 2, they will be removed from study.

4.3 END OF TREATMENT AND TREATMENT TERMINATION VISITS

An end of treatment (EOT) visit is required for all subjects within 14 days after the last dose of study drug.

The Schedule of Assessments (Appendix 1) describes the procedures required for EOT visit.

4.4 FOLLOW-UP FOR PROGRESSION AND SURVIVAL

Patients will be followed every 12 weeks for 52 weeks for EFS and PFS after the EOT visit, removal from study, or until death, whichever occurs first. Follow up can include CBC, CMP, LDH and CT and/or PET/CT per standard of care. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Patients who discontinue study treatment because of PD will enter overall survival (OS) follow-up and will be contacted every 12 weeks for 52 weeks for survival status.

4.5 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

5 STATISTICAL METHODS OF ANALYSIS

5.1 GENERAL CONSIDERATIONS

The primary objective of phase II study is to evaluate the CR rate of acalabrutinib + R-ICE x 3 cycles according to fluorine18 -fluorodeoxyglucose PET imaging criteria. The CR/CRu rate of R-ICE in previously rituximab exposed patients on the CORAL study was 29% (personal communication with Christian Gisselbrecht, CORAL PI). To this end, an optimal Simon two-stage design will be utilized. Given the historic control, we will set the desirable CR rate as 50% or higher for the proposed new treatment regimen, and 30% or lower as undesirable. In the first stage, we will enroll 20 eligible patients. If 6 or fewer patients achieve CR after 3 cycles, no additional patients will be enrolled and the regimen will be considered not promising. If 7 or more patients achieve CR, then an additional 26 patients will be enrolled for the second stage. Among the total 46 patients, if 18 or more patients are able to achieve CR

then this treatment regimen will be considered promising. This decision rule has a one-sided type I error (declaring the new treatment regimen promising while it is actually not) rate as 0.10 and a type II error (declaring the new treatment regimen not promising while it actually is) rate as 0.10.

The study includes a number of secondary objectives. Descriptive statistics will be used to summarize the safety profile of the treatment regimen, and summarize the mobilization rates. Kaplan-Meier methodology will be used to estimate overall and progression-free survival. The association between genetic markers, MTV, ctDNA, and disease response will be assessed.

5.2 ENDPOINT DATA ANALYSIS

5.2.1 Efficacy Endpoint(s)

The primary endpoint is complete response rate at the end of cycle 3 of treatment. Secondary endpoints are toxicity and adverse event rates, PR and OR rates at the end of cycle 3, as well as PFS, EFS, and OS at 1 year.

5.2.2 Safety Endpoint(s)

- Safety and tolerability of acalabrutinib with R-ICE in patients with rel/ref DLBCL

5.2.3 Study Treatment Administration and Compliance

Descriptive information will be provided regarding the number of acalabrutinib doses prescribed, the total number of doses taken, the number of days of treatment, and the number and timing of prescribed dose delay, reductions and interruptions.
For each subject, acalabrutinib compliance will be described in terms of the proportion of study drug actually taken.

5.2.4 Analysis of Efficacy Parameters

Analysis of efficacy parameters will be evaluated using the efficacy parameters defined in section 3.1.1 using the RECIL response criteria outlined in 4.1.16.

5.2.5 Primary Efficacy Endpoint

CR rate will be calculated along with an exact 95% CI based on binomial distribution.

5.2.6 Secondary Efficacy Endpoint

ORR and PR rates will be calculated along with exact 95% Cis based on binomial distribution.
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, or have discontinued the study will be censored on last assessment (or, if no post-baseline tumor assessment, at the time of first dose plus 1 day). Duration of PFS will be estimated using Kaplan-Meier methodology. Approximate 95% CIs for median duration of PFS will be computed using the formula proposed by Brookmeyer and Crowley.
EFS is defined as the time from first dose to documented disease progression, death from any cause, or study dropout, whichever occurs first. Duration of EFS will be estimated using Kaplan-Meier methodology. Approximate 95% CIs for median duration of EFS will be computed using the formula proposed by Brookmeyer and Crowley.
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. Duration of OS will be estimated using Kaplan-Meier methodology. Approximate 95% CIs for median duration of OS will be computed using the formula proposed by Brookmeyer and Crowley.

5.2.7 PK, PD or Biomarker Analyses

Baseline MTV, end of treatment MTV, and baseline ctDNA will be associated with CR, PR, and ORR by Wilcoxon rank sum tests. Baseline and post treatment mutations detected by NGS will be associated

with CR, PR, and ORR by Fisher's exact tests. MTV (baseline and end of treatment) and mutations (baseline and post treatment) will be associated with EFS, PFS, and OS using Cox regression treating MTV as time-dependent covariate. Baseline ctDNA will be associated with EFS, PFS, and OS by log-rank tests.

6 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording DLTs, AEs, and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).]

6.1 DEFINITIONS

6.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the condition being studied that were not present before the AE reporting period.
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Abnormal laboratory values considered clinically significant by the investigator should be reported as an AE.

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.]

6.1.2 Serious Adverse Event

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the supplier of the study medication to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 of the following criteria:

- It results in death (ie, the AE actually causes or leads to death).
- It is life-threatening (ie, the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).]

6.1.3 Severity

Definitions found in the CTCAE version 5 will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- 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]

6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the CRF.

6.2.1 Adverse Event Reporting Period

The AE reporting period for this study begins when the subject receives the first dose of study drug and ends 30 days after the last dose. An exception to this reporting period is any AE occurring due to a protocol-defined screening procedure. If any SAE occurs beyond 30 days after the last dose of acalabrutinib ***AND*** it is assessed by the investigator as related to acalabrutinib, it must be reported as an SAE.

6.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means, will be recorded in the subject's medical record and on the AE CRF.

Disease progression itself is not considered an AE; however, signs and symptoms of disease progression may be recorded as AEs or SAEs.

Each recorded AE or SAE will be described by its diagnostic term, duration (eg, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (see following guidance), and any actions taken. The relationship of AEs to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' per FDA guidance on safety reporting requirements (FDA Guidance 2012).

See Appendix 4 for more detail on assessing relationship.

6.2.3 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. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the CRF. For multi-center studies: If the associated AE fulfills serious criteria, Investigators should report the event to the supplier of the study medication within 24 hours using the SAE Reporting Form. The supplier of the study medication should report any SAEs to the IRB and Regulatory Authorities per institutional and/or regulatory guidelines, and to Acerta-Pharma per contractual guidelines.

In the event of subject ingestion of more than the recommended acalabrutinib dosage, observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion of acalabrutinib is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.]

6.2.4 Pregnancy

The investigator should report all pregnancies and pregnancies in the partners of subjects within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to Acerta Pharma Drug Safety. Any pregnancy-associated SAEs must be reported to Acerta Pharma, according to the usual timelines and directions for SAE reporting (Section 6.2.6).

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 this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days [2-day guidance applicable to acalabrutinib monotherapy only] after the last dose of study medication will be reported, followed to conclusion, and the outcome reported.

A pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy

(eg, congenital abnormalities/birth defects/spontaneous miscarriage or any other serious events) must additionally be reported as such using the SAE report form.
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.
Upon completion of the pregnancy, additional information on the mother, pregnancy, and baby will be collected and sent to AEMailboxClinicalTrialTCS@astrazeneca.com .
The supplier of the study medication should report all pregnancies and pregnancies in the partners of subjects to the IRB and Regulatory Authorities per institutional and/or regulatory guidelines, and to Acerta Pharma per contractual guidelines.

6.2.5 AE/SAE Reporting

6.2.5.1 AE/SAE Reporting by Study Sites to Lead Principal Investigator

The University of Miami Office of the Vice Provost for Research and Scholarship (UM OVPRS) requires expedited reporting of SAEs meeting specific criteria to worldwide regulatory authorities. Therefore, UM OVPRS must be notified immediately regarding any SAE that occurs after informed consent is obtained from subjects participating in clinical research studies.

All SAEs must be reported to the SAE Review team by phone or email within 24 hours of any person at the investigational site becoming aware of the event:

The study site will a transmit a Serious Adverse Event Report (SAER) to the SAE review team by email within 24 hours. Contact details will be provided to all sites. An optional initial report can be made via telephone, but a completed SAER must still be emailed within 24 hours of the site's knowledge of the event. The Investigational site will be provided with SAE Report forms wherein the following information is requested.

- Subject identification, Investigator name, and site number
- SAE information: event term, onset date, CTCAE grade, and causal relationship
- The outcomes attributable to the event (e.g., death, a life-threatening AE, inpatient hospitalization, prolongation of existing hospitalization, a persistent or significant disability or incapacity, or other important medical event[s])
- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history
- The first and last dates of study drug administration. NOTE: as this is a Open label randomized study,
- Indicate if the study drug was discontinued or the study drug administration schedule modified
- Supplemental information may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates

In addition, applicable case report form pages should be appended to communicate relevant study drug and subject outcome information. The SAE Report should be emailed within 24 hours with as much of the above listed information as available at the time. The following minimum information is required for reporting an SAE: subject identification, reporting source, and an event or outcome. Supplemental

information may be transmitted using a follow-up report and should not delay the initial report. The Sponsor may contact the investigational site to solicit additional information or follow up on the event.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the applicable pages of the subject's eCRF.

UM OVPRS will report to Food and Drug Administration (FDA) any applicable SAEs.

6.2.6 Expedited Reporting Requirements for Serious Adverse Events

The LEAD PRINCIPAL INVESTIGATOR shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this section, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

All SAEs must be reported to Acerta Pharma/Astra Zeneca within 7 days of discovery for fatal and life-threatening reports (15 days for other SAE and special situation reports) and to the IRB/IEC <<per their requirements.>> Acerta Pharma/Astra Zeneca may request follow-up and other additional information from the investigator.

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

If study drug is discontinued because of an SAE, this information must be included in the SAE report. An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product and is not listed in the current Investigator Brochure (i.e., an unexpected event).

	Drug Safety Contact Information
Fax:	+1 866 467 0304 or +1 650 965 4996
Email:	AEMailboxClinicalTrialTCS@astrazeneca.com

The lead principal investigator should report all SAEs to the IRB and Regulatory Authorities per institutional and/or regulatory guidelines, and to Acerta Pharma/AstraZeneca per contractual guidelines. For Sponsors with subsites: Investigators should report any SAEs to investigational Sponsor within 24 hours using the SAE Reporting Form.

Generally, any AE considered serious by the PI or Sub-investigator or which meets the definition of an SAE included in **Section 6.1.2, Serious Adverse Events.**

SAEs will be captured on the appropriate case report form (CRF) as well as in the Serious Adverse Event reporting section in Velos, a HIPAA AND 21 CFR part 11 compliant database and will be reported to the University of Miami's IRB per institutional requirements.

6.2.7 AE/SAE Reporting by Lead PI to U.S. Regulatory Authorities

According to 21 CFR 312.32(c)(1), "the sponsor [lead PI] must notify FDA in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later

than 15 calendar days after the sponsor [lead PI] determines that the information qualifies for reporting. In each IND safety report, the sponsor [lead PI] must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. The sponsor [lead PI] must report any suspected adverse reaction that is both serious and unexpected. The sponsor [lead PI] must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

> (A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
> (B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
> (C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group."

Furthermore, according to 21 CFR 312.32(c)(2), "the sponsor [lead PI] must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's [lead PI's] initial receipt of the information."

6.2.8 Type and Duration of Follow-up of Subjects after Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent.

7 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

The Sponsor retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- *Unsatisfactory subject enrollment with regard to quality or quantity*
- *Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects and maintain adequate study records*
- *Inaccurate, incomplete and/or late data recording on a recurrent basis*
- *The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment*

7.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the informed consent, current Investigator Brochure, and any other relevant supporting information (eg, all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, before the implementation of changes in this study.

This clinical study was designed and will be implemented in accordance with the protocol, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practices, applicable local regulations (including US Code of Federal Regulations (CFR) Title 21 and European Directive 2001/20/EC), and the ethical principles laid down in the Declaration of Helsinki.

7.2 SUBJECT SCREENING LOG

The investigator will keep a record that lists all subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

7.3 CASE REPORT FORMS

Authorized study site personnel will complete CRFs designed for this study according to the completion guidelines that will be provided within the clinical database. The investigator will ensure that the CRFs are accurate, complete, legible, and completed promptly.

7.4 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

Acalabrutinib capsules will be supplied to the site research or investigational pharmacy department. The study drug must not be used outside the context of the protocol. Refer to the Manual of Procedures for further information.

7.5 RECORD RETENTION

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each Form FDA 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE information, subject files (source documentation) that substantiate entries in CRFs, all relevant correspondence and other documents pertaining to the conduct of the study.
The investigator shall retain study records in accordance with institutional and/or national/local regulations, whichever is longer.
All patients will be requested to maintain a medication diary of each dose of acalabrutinib (Appendix 6). Medication diaries and pill bottles (including remaining or missed capsules) will be returned to research staff at the end of each cycle for reconciliation and completion of drug return forms.

7.6 DISCLOSURE AND PUBLICATION POLICY

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential.

The financial disclosure information will be completed prior to trial participation from all PIs and Sub-Investigators who are involved in the trial and named on the FDA 1572 form.

The lead principal investigator will register the trial on www.clinicaltrials.gov. In addition, the lead principal investigator will publish the results of the trial.

8 REFERENCES

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Parameter	Pre-treatment Period Screening	Open-Label Treatment Period			Follow-Up[n]
In Clinic	Up to 28 days before enrollment	Cycle 1, Day 1 Cycles 2 to 3 (Day 1,+ 7 or – 3 days)	Response Evaluation Cycle 2	End of Treatment Visit[a] (14 – 28 days after last dose of study drug)	Every 12 weeks (+ or – 1 week) for 52 weeks
Screening/Administrative					
Informed Consent	X				
Demographics/ Medical History	X				
Inclusion/Exclusion	X				
Staging and sAAIPI	X				
Patient diary will be provided	X[o]				
Check patient medication diary for treatment compliance		X			
Study Drug Administration					
Acalabrutinib administration		Refer to Dose and Administration – Section 3.5 3			
R-ICE administration		Refer to Dose and Administration – Section 3.5 3			
Safety Assessments					
Complete physical examination	X[k]				
Directed physical examination with lymphoma symptoms reviewed and recorded[b]		X[b, l]		X	
Performance status (ECOG)	X[k]	X		X	
Vital Signs (heart rate, temperature, BP)	X[k]	X		X	
Weight	X[k]	X		X	
Height	X[k]				
BSA		X			
ECG	X			X	
Echocardiogram/MUGA scan[c]	X				
Concomitant Medications	←——————X——————→				
Adverse Events	←——————X——————→				X
Clinical Laboratory Assessments					
Hematology (CBC with differential: WBC, HGB, HCT, platelet count, ANC, ALC)	X[k]	X[e]		X	
Chemistry (albumin, ALP, ALT, AST, CO_2, BUN, Ca, Cl, creatinine, glucose, LDH, Mg, phosphate/phosphorus, K, Na, total bilirubin, total protein, uric acid)[d]	X[k]	X[f]		X	
Chemistry (K)		X[l]			
Urinalysis		X[l]			
Coagulation panel (PT, aPTT, INR)	X				
HBV surface antigen and HCV (antibodies)	X				
Serum or urine β-HCG pregnancy test (for females with childbearing potential)	X[e]			X	
Total cell count, B cell count	X			X	

Parameter	Pretreament Period Screening	Open-Label Treatment Period			Follow-Up[n]
In Clinic	Up to 28 days before enrollment	Cycles 1 to 3 (Day 1)	Response Evaluation Cycle 2	End of Treatment Visit[a]	
Efficacy Assessments					
CT imaging (neck, chest, abdomen, and pelvis) with IV or oral contrast	X[h]		X[h]	X[i]	
Whole body FDG-PET scan[h, i]	X[h]			X[i]	
Evaluation of other sites of disease[h, i]	X			X	
Bone marrow biopsy[j]	X				
ctDNA assessment[m]	X			X	
Survival					X

ALC=absolute lymphocyte count; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AP=alkaline phosphatase; aPTT= activated partial thromboplastin time; AST=aspartate aminotransferase; β-HCG=beta-human chorionic gonadotropin; BP=blood pressure; BSA=body surface area; BUN-blood urea nitrogen; Ca=calcium; Cl=chloride; CO_2=bicarbonate; CT=computed tomography; ctDNA= circulating tumor DNA; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FDG=fluorodeoxyglucose; HBV=hepatitis B virus; HCV=hepatitis C virus; IHC=immunohistochemistry; INR= international normalized ratio; IV=intravenous; K=potassium; LDH=lactate dehydrogenase; Mg=magnesium; MUGA=multiple-gated acquisition scan; Na=sodium; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetics; PT=prothrombin time; R-ICE=rituximab, ifosfamide, carboplatin, and etoposide; sAAIPI= age-adjusted international prognostic index at the initiation of second-line therapy;WBC=white blood count.

a	This visit is required for all subjects. It should take place 14-28 days after the last dose of study drug.
b	Directed physical examination includes all organ systems that were previously abnormal or involved with disease and documentation of any clinically relevant abnormalities in any organ. Lymphoma symptoms reported at screening should be reviewed and recorded during the directed physical examination. Subjects should be questioned regarding changes in ocular status and referred to an ophthalmologist for a formal exam if any positive findings (Grade ≥2) are reported.
c	Echocardiography or MUGA scan is mandatory at baseline; thereafter it can be repeated optionally at any time during the study if clinically relevant, or in case of cardiac adverse events, using the same modality as at baseline.
d	Calculated creatinine clearance of ≥60 mL/minute/1.73 m^2 within 14 days before enrollment.
e	Samples can be taken on the day of or day prior to dosing, provided that results are available before the dose of study drug is given. Hematology should be done on Days 1, between Days 7 and 10, and on Day 14 of each cycle with a window of ±1 day. For pregnancy tests, if the pregnancy test during screening is within 28 days of Cycle 1 Day 1, it does not need to be repeated.
f	Samples can be taken on the day of or day prior to dosing. The results do not need to be available before the dose of study drug is given.
g	Computed tomography and PET scans obtained for standard subject evaluations before signing ICF can be used for screening, but should not be older than 28 days prior to enrollment.
h	Computed tomography scan and PET scans will be performed at screening and at the end of Cycle 3. CT scan will occur Day 15-21 of Cycle 2 to demonstrate lack of progression of disease (PD)[24]. If PD, patient will be removed from study. Positron emission tomography scans must be done between Days 15 to 21 of Cycle 3.
i	Computed tomography and PET scans are required at early withdrawal. Computed tomography and PET scans performed after Cycle 3 are considered the End-of-Treatment disease efficacy assessment (or earlier if <3 cycles administered as per investigator discretion). If early withdrawal prior to the end of Cycle 3, CT and PET scans are to be repeated.
j	Morphological and IHC examination of the bone marrow is required and should be performed within 28 days prior to the first dose of study drug. In subjects with bone marrow involvement prior to treatment, bone marrow biopsy must be repeated once during the study for confirmation of CR (preferentially within 30 days of initial documentation of CR). Bone marrow obtained for standard subject evaluations before signing ICF can be used for screening, but should not be older than 28 days prior to treatment.
k	If this visit occurs within 7 days of Cycle 1 Day 1. It may be used for the screening and Cycle 1 Day 1 treatment evaluations.
l	A directed physical exam, chemistry (potassium) and urinalysis assessments will be performed every day while participants are receiving R-ICE treatment.
m	RNB for patients with evaluable clonotype determined on pretreatment tumor specimen. Required ctDNA assessment time points: pre-treatment, and at EOT.
n	Follow-up every 12 weeks for 52 weeks after EOT visit, until removal from study, or until death. SAEs considered related to study drug should be documented
o	A patient diary will be provided to participants and study team members will advise participants on how to record information in the diary.

Appendix 2. Performance Status Scores

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX 3. 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 4. Adverse Event Assessment of Causality

Adverse Event:_____
Is there a reasonable possibility that the event may have been caused by study drug? No___ Yes___
The descriptions provided below will help guide the principal investigator in making the decision to choose either “yes” or “no”:
No = There is no reasonable possibility that the event may have been caused by study drug.
The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject’s clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drug.
The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or preclinical data
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

APPENDIX 5. COLLECTION AND PROCESSING AND END-OF-TREAMENT BLOOD SAMPLES FOR BCR CLONOTYPING

Materials

- BD Vacutainer® Molecular Cell Preparation Tube, 8 mL (BD362761)
- DMSO (Sigma Cat. No D2650)
- IMDM- Iscove's Modified Dulbecco's Medium (Thermo Scientific Cat. No 12440-053)
- Fetal bovine serum- FBS (Thermo Scientific Cat. No 26140-079)
- HBSS- Hank's Balanced Salt Solution (Thermo Scientific Cat. No 14170-112)
- 2.0mL Cryo Storage Vial (VWR Cat. No 66008-728)
- 15mL Centrifuge Tubes (VWR Cat. No 21008-918)

Procedure

1. Blood Collection

1.1. Collect whole blood in two (2) pre-labeled BD Vacutainer Molecular Cell Preparation Tubes (CPT), 8 mL each.

1.2. Invert each tube 8-10 times at store at room temperature (18-25°C).

2. Shipping and Receiving blood samples in cell preparation tubes

2.1. Sylvester sites will coordinate with the BioSpecimen Shared Resource (BSSR; Melinda Boone and Elena Cortizas) for drop off/pick up of blood samples. *CPT processing should occur within 2 hours of collection.*

2.2. For non-Sylvester sites: Ship CPT tubes the same day via FedEx First Overnight to:
ATTN: Melinda Boone
SCCC Biospecimen Shared Resources
1550 NW 10th Ave, Fox 436
Miami, Florida 33136

Samples should be kept and shipped at room temperature. Shipments should be sent Monday – Wednesday only to avoid being delayed in transit during the weekend.

3. Freezing Medium Preparation (If necessary)

3.1. Freezing medium consists of 70% FBS, 20% IMDM, and 10% DMSO.

3.2. To prepare 50mL of freezing medium

3.2.1. Add 35mL FBS to a clean 50mL conical tube.

3.2.2. Add 10mL IMDM to the conical tube and gently invert.

3.2.3. Add 5mL DMSO to the conical tube, invert 5 times.

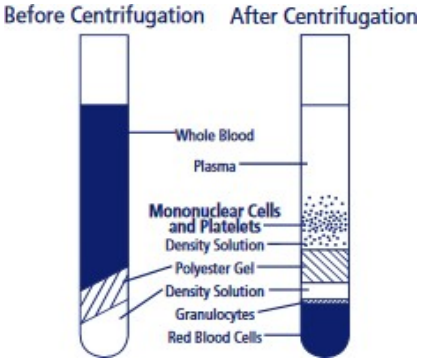
3.2.4. Aliquot 5mL into 10-15mL conicals and store at -20º C until ready for use.

4. CPT Processing

4.1. Upon arrival, make sure that CPT tube is maintained in an upright position, and kept at room temperature until centrifugation.

4.2. For optimal results, processing should be started within 2 hours of blood collection; cell degradation will occur if tubes are stored for longer than four hours.

4.3. Centrifuge CPT tubes at 1800 x g for 40 minutes at room temperature. Turn the centrifuge brake off by setting the deceleration to zero.



4.4. After centrifugation, place the CPT tube in biological safety cabinet and carefully remove the top.
4.5. Using a sterile 5mL transfer pipet, gently pipette the plasma up and down against the gel plug to dislodge cells that are stuck to the top of the gel. Avoid vigorous pipetting that would disintegrate the gel plug itself.
4.6. Transfer the cell suspension from each CPT tube (2) from a single patient time point to a 15mL conical polypropylene tube. Bring cell suspension to a final volume of 12mL with HBSS.
4.7. Transfer one aliquot of cell suspension (1 million PBMC suspended in 1 ml RPMI with 10% bovine serum) into a tube for clinical flow (see below for procedure).
4.8. Centrifuge 15mL tubes at 250 x g for 10 minutes at room temperature.

5. **Cell Resuspension/Cryopreservation**
5.1. When centrifugation is complete, aspirate the supernatant and gently flick the tube to break up the pellet.
5.2. Gently swirl cell suspension in 15mL tube and 1mL freezing media gradually.
5.3. Place the tube on ice and avoid any further mixing or agitation of the cells.
5.4. Using a sterile 5mL transfer pipet, transfer the cell suspension into a 2.0mL cryovial.
5.5. Place aliquots in a Mr. Frosty™ freezing container filled with 100% isopropyl alcohol that has been pre-cooled at -80º C and return to -80 º C. This will achieve a cooling rate of close to -1 º C/minute.
5.6. Store samples at -80º C for 24 hours, then transfer to permanent storage in liquid nitrogen.
5.7. The BSSR will store plasma/mononuclear cell layer. When enough samples have been processed and stored to batch for RNA extraction, the BSSR will contact the Onco-Genomics Shared Resource (OGSR) to coordinate pickup of samples.
5.8. The OGSR will pick up samples on dry ice and process for RNA extraction (procedure below) immediately.

RNA extraction and BCR clonotyping of pre-treatment and end-of-treatment blood samples

Materials

- RNeasy Mini Kit 50 rxns (Qiagen 74104)
- Fragment Analzyer HS/SS RNA Kit
- Qubit HS/BR RNA Kit
- ArcherDx Immunoverse HS BCR IGH/K/L kit
- Fragment Analzyer HS DNA Kit
- Qubit HS DNA Kit
- MiSeq Reagents

Procedure

1. **RNA Extraction of isolated plasma/mononuclear cell layer following manufacturer's protocol.**
   1.1. RNeasy Mini Kit (100 ug RNA) (Qiagen 74104)

2. **RNA Quantification and QC**
   2.1. Run 2 ul of extracted total RNA on Fragment Analyzer using the High Sensitivity/Standard Sensitivity RNA Kit.
   2.2. Visualize quality and record RIN score.
   2.3. Run 2 ul of extracted total RNA on Qubit Fluorometer to determine concentration.

3. **Prepare sequencing library using the ArcherDx Immunoverse HS BCR IGH/K/L kit following the manufacturer's protocol.**
   3.1. For pre-treatment samples, the input is 400 ng of RNA.
   3.2. For end-of-treatment samples, the input is 1600 ng of RNA.

4. **Library Quantification and QC**
   4.1. Run 2 ul of library on Fragment Analyzer using the High Sensitivity DNA kit.
   4.2. Visualize quality of library and record average fragment size.
   4.3. Run 2 ul of library on Qubit Fluorometer to determine concentration.

5. **Sequencing**
   5.1. Libraries will be pooled and sequenced on an Illumina MiSeq (2x300 bp).
   5.2. Pre-treatment libraries will be sequenced at 1 million read-pairs per sample.
   5.3. Post-treatment libraries will be sequence at 4 million read-pairs per sample.

6. **Data Analysis**

MRD assessment for normalization with blood samples

Procedure

1) An aliquot from the plasma/mononuclear cell layer will be immediately transfer to Hematopathology by the Biospecimen Shared Resource.
2) Hematopathology will run clinical flow cytometry procedure.

Collection of circulating cell free DNA (ccfDNA) of pre-treatment and end-of-treatment samples

Materials

- PAXgene ccfDNA blood tube (PreAnalytix 768115)
- QIAamp MinElute ccfDNA Mini (Qiagen 55204)
- Fragment Analyzer HS DNA Kit
- Qubit HS DNA Kit

Procedure

1. Pre-label two (2) PAXgene ccfDNA blood tubes (10mL) per patient.

1.1. Collect whole blood in a PAXgene ccfDNA blood tube to its' maximum volume.
1.2. Invert tube 8 times to mix blood and additive.
1.3. Immediately store at 4°C. *(The whole blood sample can be stored for up to 10 days at temperatures from 2°C to 25°C, 7 days at up to 30°C, and 3 days at up to 37°C prior to processing. Do not store below 2°C)*

2. Shipping and receiving blood samples in PAXgene tubes

2.1. For Sylvester sites, collected samples will be received by the BSSR along with the above CPT blood tubes for plasma/mononuclear cells isolation.
2.2. For Non-Sylvester sites, …
2.3. The BSSR will store the PAXgene ccfDNA blood tubes at 4°C.
2.4. Due to time restrictions on processing these tubes, the BSSR will contact the OGSR upon arrival and storage of samples to arrange retrieval.
2.5. The OGSR will receive the samples from the BSSR and store at 4°C until processing within the time frame based on sampling date and temperature storage.

3. ccfDNA Isolation

3.1. The whole blood sample will following the manufacturer's protocol for Plasma Preparation Isolation of ccfDNA in PAXgene ccfDNA blood tube prior to ccfDNA isolation.
3.2. ccfDNA Isolation will following the manufacturer's protocol
3.2.1. QIAamp MinElute ccfDNA Mini (Qiagen 55204)

4. ccfDNA Quantification and QC

4.1. Run 2 ul of ccfDNA on Fragment Analyzer using the High Sensitivity DNA kit.
4.2. Visualize quality of ccfDNA.
4.3. Run 2 ul of ccfDNA on Qubit Fluorometer to determine concentration.

5. The ccfDNA will be stored at -20°C.