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TITLE: A Phase 2 Study of acalabrutinib in combination with lisocabtagene maraleucel in relapsed/refractory aggressive B-cell lymphomas

Sponsor-Investigator: **Patrick Connor Johnson, MD**
Massachusetts General Hospital
pcjohnson@mgh.harvard.edu

Principal Investigators (PI): **Patrick Connor Johnson, MD**
Massachusetts General Hospital
pcjohnson@mgh.harvard.edu

Statistician:
Robert Redd
Dana-Farber/Harvard Cancer Center
robert_redd@dfci.harvard.edu

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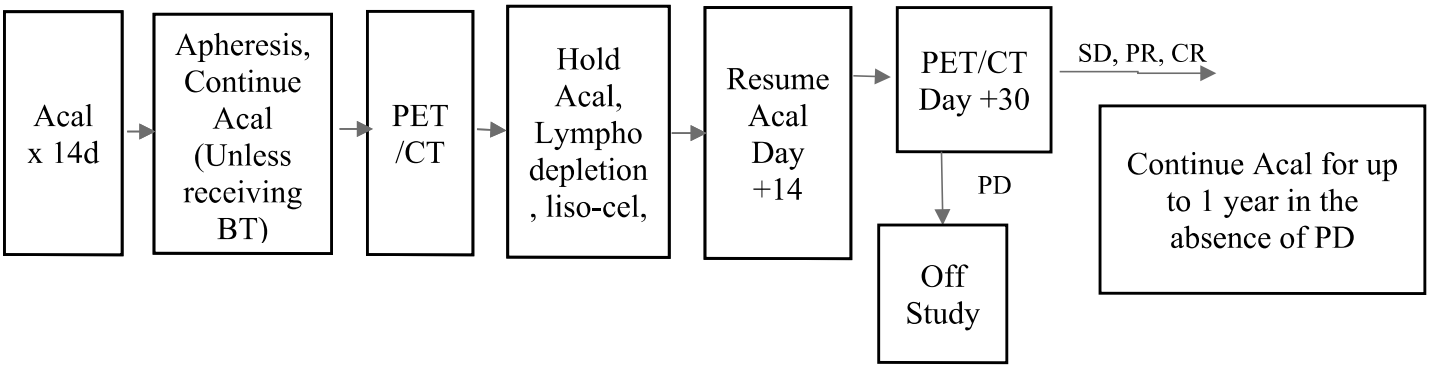
SCHEMA



Acal = Acalabrutinib; Liso-cel = Lisocabtagene maraleucel; BT = bridging therapy
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

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1. OBJECTIVES

1.1 Study Design

This is a phase II single arm study with a single stage design to assess the efficacy and safety of acalabrutinib combined with lisocabtagene maraleucel for relapsed/refractory aggressive B-cell lymphomas. 27 patients with relapsed/refractory aggressive B-cell lymphomas will be enrolled.

1.2 Primary Objectives

The primary objective of this study is to estimate the clinical efficacy of acalabrutinib plus lisocabtagene maraleucel in adult subjects with relapsed/refractory aggressive B-cell lymphomas. The primary endpoint of this study is the complete response rate after lisocabtagene maraleucel and acalabrutinib treatment.

1.3 Secondary Objectives

The secondary objectives of this study are to assess the safety and clinical efficacy of acalabrutinib plus lisocabtagene maraleucel, and to characterize the impact of the combination of acalabrutinib plus lisocabtagene maraleucel on quality of life and health care utilization. The secondary endpoints of the study include the overall response rate of acalabrutinib plus lisocabtagene maraleucel in adult subjects with relapsed/refractory aggressive B-cell lymphomas at 3, 6, and 12 months after lisocabtagene maraleucel treatment, progression-free survival, overall survival, event-free survival, duration of response, rates of bridging therapy use, rates of acalabrutinib discontinuation due to toxicity, incidence of adverse events, incidence of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), intensive care unit (ICU) admission rates during treatment with lisocabtagene maraleucel, re-hospitalization rates at 3 months after lisocabtagene maraleucel treatment, median hospital length of stay lisocabtagene maraleucel treatment, health-care related quality of life 1 and 6 months after lisocabtagene maraleucel treatment measured using the Functional Assessment of Cancer Treatment-General (FACT-G).

1.4 Exploratory Objectives

The exploratory objectives of this study are to determine the pharmacokinetics of acalabrutinib plus lisocabtagene maraleucel, to assess the quality of T-cell collections with acalabrutinib therapy using flow cytometry-based phenotyping and transcriptional analysis, and to compare the efficacy of the combination of acalabrutinib plus lisocabtagene maraleucel among different types of Non-Hodgkin lymphoma. Exploratory endpoints are the immunophenotypic and genomic profile and functional activity of collected T-cells, the immunophenotypic and genomic profile and functional activity of CAR T-cells after acalabrutinib, overall response rate of acalabrutinib plus lisocabtagene maraleucel in aggressive B-cell lymphoma subtypes, complete response rate in aggressive B-cell lymphoma subtypes, progression-free survival and overall survival in aggressive B-cell lymphoma subtypes.

2. BACKGROUND

2.1 Aggressive B-cell non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) is the seventh-most common cancer in the United States, with approximately 77,000 new cases and 20,000 deaths estimated in the United States in 2020[1]. A substantial proportion of these cases are aggressive B-cell lymphomas[2], which are often curable with standard chemoimmunotherapy[3-5], but outcomes have been poor for patients with relapsed/refractory disease. Patients relapsing after initial treatment have typically been approached based on their candidacy for intensive chemotherapy and stem cell transplant with curative intent, while patients felt unfit for high dose chemotherapy have been treated with palliative intent. Even among patients considered eligible for intensive therapy, however, fewer than half will actually proceed to stem cell transplantation, primarily because of failure to demonstrate sufficient chemosensitivity to second line therapies[6-12]. Patients with chemotherapy-refractory disease or those with relapse after second-line therapy have a historically dismal prognosis, with a median survival of approximately six months[13].

CAR T-cells are autologous T-cells transduced with a chimeric antigen receptor targeted to a specified cancer antigen[14]. Anti-CD19 CAR T-cell therapy has transformed the landscape of treatment options for relapsed/refractory aggressive B-cell lymphomas[15,13]. Landmark studies utilizing three different anti-CD19 CAR T-cell products, axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel, in patients with relapsed/refractory aggressive B-cell lymphomas have demonstrated durable remissions in a significant subset of patients[12,14,16,17]. Despite this, the majority of patients will not have complete or durable remissions[14], and so these patients continue to constitute a high risk population. Thus, improving the response rates of anti-CD19 CAR T-cell therapy is a critical area of investigation.

Moreover, CAR T-cell therapy is associated with significant risks of toxicity, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Toxicities are typically manageable and reversible, but they can be severe and require care in intensive care units[14,18,19]. The rates of CRS and ICANS differ between anti-CD19 CAR T-cell products, partly related to different co-stimulation domains in the respective products[14]. Axicabtagene ciloleucel was associated with a CRS rate of 93% and ICANS rate of 64%[14,20], whereas lisocabtagene maraleucel was associated with CRS and ICANS rates of 42% and 30%, respectively[14,21]. Given the significant rates of toxicity, reducing their incidence is also a critical area of investigation.

2.2 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 and tablets per FDA approval. Acalabrutinib has been approved in the United States and other markets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL). It is also being evaluated for the treatment of patients with other B-cell malignancies.

2.2.1 Mechanism of Action

Acalabrutinib is a potent inhibitor of Bruton's tyrosine kinase (BTK). Pharmacology models have been used to define kinase selectivity of acalabrutinib in comparison to other BTK inhibitors, and to investigate functional effects of on-target and off-target activities. Acalabrutinib shows improved selectivity for BTK compared with ibrutinib[22]. Functional inhibition of non-target cells (eg, T cells, NK cells, platelets) was not observed for acalabrutinib at clinically relevant concentrations.

2.2.2 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.

Both the capsule and tablet formulations are bioequivalent and the same safety and efficacy can be expected.

2.2.3 Drug-drug Interaction Potential

For more detailed information on drug-drug interaction potential for acalabrutinib, refer to the Investigator Brochure.

Please refer to Section 7.2.2 for guidance on drugs that may cause drug-drug interactions. The new tablet formulation approved by the FDA was developed to overcome the interactions between acalabrutinib capsules and acid reducing agents (ARAs). Acalabrutinib tablets can be co-administered with all acid reducing agents (proton pump inhibitors, H2-receptor antagonists, antacids).

2.2.4 Clinical Experience

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

2.2.4.1 Clinical Efficacy

100 mg BID of acalabrutinib is used in patients with CLL and MCL[23]. This regimen has also been utilized in a number of clinical trials of various indications with acalabrutinib monotherapy in combination with other agents. Please refer to the Investigator Brochure for details.

2.2.4.2 Adverse Events

An aggregate safety analysis of acalabrutinib monotherapy was conducted in order to assess safety for acalabrutinib-exposed subjects with hematologic malignancies without confounding toxicity from combination therapy drugs. The analysis was performed on a 9-study integrated monotherapy population (hereafter called 'Mono HemMalig population'), which consisted of

treated subjects in 6 acalabrutinib monotherapy studies (ACE-CL-309, 15-H-0016, ACE-CL001, ACE-LY-002, ACE-LY-004, and ACE-WM-001) and treated subjects in the acalabrutinib monotherapy treatment arms of 3 additional combination studies (ACE-CL-007, ACE-LY-003 and ACE-MY-001). As of the 30 October 2020 data extraction date, the pooled Investigator's Brochure AstraZeneca ACP-196, Mono HemMalig population represented 1079 acalabrutinib-exposed subjects with a median exposure of 28.5 months (range: 0.0 to 65.3 months). On the basis of the analysis of data from this pooled population, the overall safety of acalabrutinib monotherapy in subjects with hematologic malignancies is considered acceptable. An overview of AEs for this population is presented in Table 1-X.

Table 1-X: Overview of TEAEs in the Mono HemMalig Population

Adverse Event Category	**No. (%) of Subjects (N=1079)**
Any treatment-emergent adverse events	
Any grade	1052 (97.5)
Grade >=3	650 (60.2)
Any adverse event related to acalabrutinib	
Any grade	792 (73.4)
Grade >=3	284 (26.3)
Any serious adverse event	466 (43.2)
Adverse events leading to study drug discontinuation	137 (12.7)
Grade 5 (fatal) adverse event	61 (5.7)

Mono HemMalig studies include ACE-CL-309, ACE-CL-007, 15-H-0016, ACE-CL-001, ACE-LY-002, ACE-LY-003, ACE-LY-004, ACE-MY-001, and ACE-WM-001. Note: A subject with multiple severity grades for the same preferred term was counted only once in the most severe grade. Data as of 30 October 2020

A total of 1052 subjects (97.5%) had at least 1 AE, and over half (650 subjects [60.2%]) had at least one Grade ≥ 3 AE. The most commonly reported AEs (≥ 20%) of any grade were diarrhea (37.7%), headache (37.4%), upper respiratory tract infection (26.3%), cough (23.6%), fatigue (23.0%), contusion (22.5%), nausea (22.2%), and arthralgia (21.3%). The most frequently reported Grade ≥ 3 AEs (≥ 2%) were neutropenia (12.0%), anemia (7.8%), pneumonia (6.3%), hypertension (3.8%), thrombocytopenia (3.5%), diarrhea (3.0%), syncope (2.4%), and dyspnea (2.0%).

Treatment-related AEs were reported for 792 subjects (73.4%), and 284 subjects (26.3%) had Grade ≥ 3 treatment-related AEs. The most frequently reported treatment-related AEs (≥ 5%) of any grade were headache (26.1%), diarrhea (17.9%), contusion (14.5%), neutropenia (9.5%), nausea (8.8%), fatigue (8.6%), arthralgia (6.9%), petechiae (6.0%), and upper respiratory tract infection (5.5%). The most frequently reported treatment-related Grade ≥ 3 AE (≥ 2%) was neutropenia (8.5%). Grade 5 AEs were reported for 61 subjects (5.7%) in the Mono HemMalig population (see Table 15). Of these 61 subjects, 22 subjects (2.0%) had an infection event, including 8 subjects (0.7%) with Grade 5 pneumonia, 4 subjects (0.4%) with Grade 5 septic shock, and 3 subjects (0.3%) with Grade 5 sepsis. The remaining reported Grade 5 infection events include Aspergillus infection, brain abscess, bronchitis, bronchopulmonary aspergillosis, Candida sepsis, lung infection, and respiratory tract infection (1 subject each [0.1%]). Multiple organ dysfunctional syndrome and respiratory failure were reported in 2 subjects each (0.2% each), and all other Grade 5 AEs were reported in 1 subject each. In the Mono HemMalig population, 5 subjects experienced fatal AEs that were considered by the investigator to be related to study treatment. These events included intracranial hematoma (Study ACE-WM-001), hepatic failure (Study 15-H-0016), febrile neutropenia (Study ACE-CL-007), malignant brain

neoplasm (Study ACE-CL-309), and pneumonia (Study ACE-CL-309)

For more comprehensive information on the safety profile of acalabrutinib, refer to the current Investigators Brochure.

2.3 Lisocabtagene maraleucel

Lisocabtagene maraleucel (liso-cel) is a novel, anti-CD19, autologous, defined composition, chimeric antigen receptor (CAR) modified T-cell immunotherapy which is manufactured from autologous peripheral blood mononuclear cells (PBMCs) that are obtained via standard leukapheresis collection procedures. The PBMCs undergo sequential positive selection for CD8+ and CD4+ T cells where the CD4 and CD8 purified T cell populations derived from the same starting material (leukapheresis) are separated, cryopreserved, transduced with CAR and expanded through parallel processing in order to ensure the final product is infused to the subjects in a defined composition. The CD19-specific CAR consists of an scFv binding domain derived from a murine CD19-specific monoclonal antibody and the 4-1BB and CD3ζ signaling domains. The truncated human epidermal growth factor receptor (EGFRt) protein is co-expressed with the Cd19-specific CAR as a cell surface protein for analytical detection of transduced T cells. Liso-cel is provided as two individually formulated CD8+CAR+ and CD4+CAR+ T cell suspensions in media containing dimethyl sulfoxide (DMSO) that are thawed and administered by intravenous (IV) infusion. Liso-cel is FDA approved for relapsed/refractory adult diffuse large B-cell lymphoma, high grade B-cell lymphoma, transformed indolent lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. In the setting of treating adults with aggressive B-cell lymphoma, it is administered in a single-dose unit containing 100 x 10^6 chimeric antigen receptor (CAR)-positive T cells following a lymphodepleting chemotherapy regimen consisting of cyclophosphamide and fludarabine. The FDA approval in adult lymphoma patients was based on the pivotal seamless design phase I-II TRANSCEND NHL 001 study (NCT02631044) which demonstrated an overall response rate of (ORR) 73% with a complete response rate (CRR) of 53%. However, in the pivotal trial of liso-cel in relapsed/refractory large B-cell lymphomas, 35% of complete responders relapsed, the vast majority within one year[21].

2.4 Rationale for acalabrutinib combined with lisocabtagene maraleucel

Bruton tyrosine kinase (BTK) inhibitors have demonstrated improved outcomes in combination with CAR T-cell therapy. BTK inhibition with ibrutinib has shown improved T-cell number and function in CLL patients[24]. Given this, the impact of BTK inhibition in combination with anti-CD19 CAR T-cell therapy is now being explored. In mantle cell lymphoma cell lines and mouse xenograft models, use of the BTK inhibitor ibrutinib in combination with anti-CD19 CAR T-cells demonstrated superior long-term disease control[25]. Prior studies in patients with CLL demonstrated that the combination of ibrutinib and anti-CD19 CAR T-cell therapy is associated with improved overall response rates, a favorable safety profile, and lower rates of CRS[26-28]. Given these findings, we need additional investigation regarding the combination of BTK inhibition and CAR T-cell therapy in other B-cell lymphoma histologies.

Acalabrutinib, a next generation BTK inhibitor, may be a preferred drug to combine with anti-CD19 CAR T-cell therapy. Acalabrutinib is a more selective inhibitor of BTK than ibrutinib[29]. Acalabrutinib demonstrated improved tolerability compared to ibrutinib and has been utilized in patients who cannot tolerate ibrutinib therapy[30]. Moreover, acalabrutinib has already demonstrated a more favorable toxicity profile than ibrutinib in a randomized controlled trial[31], and in the pivotal trial of acalabrutinib in relapsed/refractory mantle cell lymphoma, grade 3 or higher neutropenia occurred in only 10% of patients, grade 3 or higher thrombocytopenia occurred in only 5% of patients[23]. Recently, acalabrutinib as well as ibrutinib in combination with liso-cel product demonstrated improved CD19+ tumor clearance and prolonged survival of tumor-bearing mice[32]. Thus, acalabrutinib in combination with liso-cel is a promising therapeutic strategy with the potential to augment response rates and mitigate toxicity. BTK inhibition has further demonstrated therapeutic efficacy in relapsed/refractory diffuse large B-cell lymphomas, particularly in the non-GCB subtype, providing additional rationale for response in this subgroup of patients with high risk relapsed DLBCL.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Inclusion Criteria

1. Adult patients ≥ 18 years with histologically confirmed aggressive B-cell NHL including diffuse large B-cell lymphoma (DLBCL), either de novo or transformed from any indolent B-cell lymphoma, DLBCL NOS, T cell/histiocyte-rich large B-cell lymphoma, Epstein-Barr virus [EBV] positive DLBCL NOS, primary mediastinal [thymic] large B-cell lymphoma (PMBCL), high grade B-cell lymphoma NOS, or high grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements [double/triple-hit lymphoma (DHL/THL)]; and grade 3B follicular lymphoma. Patients with primary CNS lymphoma are not eligible. Patients with secondary CNS involvement by lymphoma are eligible if they otherwise meet all eligibility criteria.

2. Relapsed or refractory to at least 2 prior lines of systemic lymphoma therapy. Previous therapy must have included a CD20-targeted agent and an anthracycline or alkylating agent.
   OR
   Relapsed or refractory to 1 prior line of systemic lymphoma therapy if relapse/refractory within 12 months of initial treatment.
   OR
   Relapsed or refractory to 1 prior line of systemic lymphoma therapy at any time after initial treatment if patient is ineligible for a transplant.

3. PET-positive measurable disease per Lugano criteria

4. ECOG Performance status 0-2

5. Estimated creatinine clearance of ≥30 mL/min, calculated using the Cockcroft and Gault equation (if male: [140 – Age] x Mass [kg] / [72 x creatinine g/dL]; multiply by 0.85 if female)

6. Serum Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≤ 3 times the ULN

7. Total Bilirubin ≤1.5 x ULN, unless directly attributable to Gilbert-Meulengracht syndrome

8. Hemodynamically stable and Left Ventricle Ejection Fraction (LVEF) ≥ 40% confirmed by echocardiogram or Multigated Radionuclide Angiography (MUGA)

9. For subjects with atrial fibrillation, atrial fibrillation must be controlled and asymptomatic

10. Absolute neutrophil count (ANC) ≥ 1000/mm^3

11. Platelets ≥ 50,000/mm^3

12. Adequate pulmonary function, defined as ≤ CTCAE Grade 1 dyspnea and SaO2 > 91% on room air

13. Woman of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib.

14. Willing and able to participate in all required evaluations and procedures in this study protocol.

15. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information.

3.1.2 Exclusion Criteria

1. History of prior malignancy that could affect compliance with the protocol or interpretation of results, except for the following:
    - Curatively treated basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix or carcinoma in situ of the prostate at any time prior to study.
    - Other cancers not specified above that have been curatively treated by surgery and/or radiation therapy and from which subject is disease-free for ≥3 years without further treatment.

2. Evidence of disease (such as severe or uncontrolled systemic diseases, including uncontrolled hypertension and renal transplant) that, in the investigator's opinion, make it

undesirable for the patient to participate in the study or that would jeopardize compliance with the protocol

3. History of or ongoing confirmed progressive multifocal leukoencephalopathy (PML)

4. Received any investigational drug within 30 days or 5 half-lives (whichever is shorter) before first dose of study drug.

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

6. Concurrent participation in another therapeutic clinical trial, with the exception of the Liso-cel out of specification and radiation trials.

7. Current life-threatening illness, medical condition, or organ system dysfunction which, in the Investigator's opinion, could compromise the subject's safety or put the study at risk

8. Previous treatment with gene therapy product or adoptive T cell therapy

9. Allogeneic stem cell transplant within 90 days of leukapheresis

10. Active acute or chronic GVHD

11. HIV infection

12. Serologic status reflecting active hepatitis B or C infection
    - Subjects who are hepatitis B core antibody (HBcAb) positive and who are hepatitis B surface antigen (HBsAg) negative will need to have a negative PCR result before enrollment and must be willing to undergo DNA PCR testing during the study. Those who are HBsAg-positive or hepatitis B PCR positive will be excluded.
    - Subjects who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis C PCR positive will be excluded.

13. Any active significant infection (e.g., bacterial, viral, or fungal, including subjects with positive cytomegalovirus [CMV] DNA polymerase chain reaction [PCR])

14. Clinically relevant CNS pathology

15. History of cardiovascular conditions within the past 6 months, including class III or IV heart failure as defined by New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or clinically significant arrhythmias: Participants with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, participants should be class 2B or better.

16. Autoimmune disease requiring chronic systemic corticosteroids at a dose of greater than 10 mg of prednisone daily or an equivalent dose of another corticosteroid

17. Treatment with alemtuzumab within 6 months leukapheresis or fludarabine or cladribine within 3 months of leukapheresis

18. Therapeutic anticoagulation

19. Bleeding diathesis

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

21. Known history of hypersensitivity or anaphylaxis to study drug(s) including active product or excipient components.

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

23. The use of strong CYP3A inhibitors within 1 week or strong CYP3A inducers within 3 weeks of the first dose of study drug is prohibited

24. Prothrombin time (PT)/INR or aPTT (in the absence of lupus anticoagulant) >2x ULN.

25. Requires treatment with proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole) if receiving acalabrutinib capsules. Note: Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study, and subjects requiring treatment with proton pump inhibitors who receive acalabrutinib tablets are permitted on study given that acalabrutinib tablets can be co-administered with all acid reducing agents.

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

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

28. Breastfeeding or pregnant: Pregnant women are excluded from this study because acalabrutinib is an agent 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, breastfeeding should be discontinued if the mother is treated with acalabrutinib.

3.2 Inclusion of Women and Minorities

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

4. REGISTRATION

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI) of the registering site. If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

4.1 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Treatment Regimen

This study will be a phase II single arm study with a single stage design to assess the efficacy and safety of acalabrutinib combined with liso-cel for relapsed/refractory aggressive B-cell lymphomas. Acalabrutinib 100 mg twice daily will begin two weeks prior to apheresis for CAR T-cell manufacturing and will be held a minimum of 24 hours prior to lymphodepleting chemotherapy and the first 14 days following liso-cel infusion (resuming day +14). Patients with rapidly progressive disease who cannot safely wait for a 2-week lead-in period in the opinion of their treating investigator may proceed immediately with apheresis along with concurrent acalabrutinib.

Liso-cel will be administered at standard target dose of 100 x 10^6 CAR-positive viable T cells (range 50 to 110 × 106 CAR positive viable T cells) after lymphodepleting chemotherapy is given, and acalabrutinib will be resumed on day +14 and continued without interruption for up to one year in the absence of progression or intolerance. Criteria for resumption of acalabrutinib are described in Section 5.2.2. A PET/CT will be performed immediately prior to beginning lymphodepleting chemotherapy, and at day +30, +90, +180, and +360. Acalabrutinib will be administered as an outpatient or inpatient (if the patient is admitted to the hospital), and liso-cel will be administered on an inpatient or outpatient basis at the discretion of the treating physician and per institutional routine.

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

The participant will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff when they come in for protocol timepoint visits..

An interim global safety analysis will also be performed after the first 10 patients are enrolled. After 10 patients are enrolled, we will pause enrollment until all 10 have reached day +28. We will then have a global safety analysis including stopping rules for toxicities of special interest, including the detection of prolonged grade 3 or higher neutropenia or thrombocytopenia in 5 or more out of 10 patients, the detection of grade 3 or higher cytokine release syndrome in 3 or more out of 10 patients, or the detection of immune effector cell-associated neurotoxicity syndrome in 3 or more out of 10 patients. In the pivotal TRANSCEND NHL 001 trial of liso-cel, prolonged grade 3 or higher cytopenias occurred in 37% of patients, grade 3 or higher CRS occurred in 2% of patients, and grade 3 or higher ICANS occurred in 10% of patients[21]; thus, these stopping rules will assess for a clinically meaningful increased risk of toxicities.

5.2 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. 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 tablets for oral administration is supplied as orange, oval, biconvex tablet with 100 mg of acalabrutinib as the active ingredient. Each tablet also contains inactive ingredients: low-substituted hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The tablet coating consists of copovidone, ferric oxide yellow, ferric oxide red, hypromellose, medium-chain triglycerides, polyethylene glycol 3350, purified water and titanium dioxide.

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.

5.2.1 Administration of Acalabrutinib

Acalabrutinib capsule and tablet is taken orally approximately every 12 hours.
The capsules and tablets should be swallowed intact with water. Subjects should not attempt to open capsules nor chew, crush, cut or dissolve the capsules and tablets 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 7.2.2. Guidance on dosing instructions on acalabrutinib when a concomitant CYP3A inhibitor is used is provided in Section 5.7.

5.2.2 Schedule for Acalabrutinib

Acalabrutinib will be started 2 weeks prior to apheresis and will be discontinued at least 24 hours prior to the initiation of lymphodepleting chemotherapy. If bridging therapy is administered, acalabrutinib must be discontinued prior to any systemic bridging therapy with a minimum washout period of 24 hours. Acalabrutinib will be restarted on day +14 in the absence of significant hematologic toxicities (grade 3 or higher neutropenia or thrombocytopenia) or any grade CRS or neurotoxicity. In the event of ongoing toxicities on day +14, acalabrutinib will not resume until the cytopenia resolves to grade 2 or better, and the CRS and/or neurotoxicity resolves entirely. Acalabrutinib will then be continued without interruption for up to one year in the absence of progression or intolerance.

5.3 Leukapheresis

Prior Anti-Cancer Treatment

No cytotoxic chemotherapy agents (e.g., cyclophosphamide) should be administered within 2 weeks of leukapheresis. Patients may not have received fludarabine, bendamustine or alemtuzumab within 6 months of leukapheresis. Bridging therapy between leukapheresis and lymphodepleting chemotherapy is allowed at the discretion of the treating investigator and is discussed in Section 5.5. Acalabrutinib will be administered as per study protocol.

Avoidance of Corticosteroids

Patients should receive no corticosteroids at a dose of greater than 10 mg prednisone daily or equivalent for 1 week prior to leukapheresis. If steroids are felt to be urgently required for disease and/or symptom control less than one week from apheresis, this may be approved in advance by the principal investigator but must be discontinued >72 hours prior to leukapheresis. No corticosteroids are allowed within 72 hours of liso-cel infusion, unless for the management of acute toxicity following liso-cel administration.

5.4 Lisocabtagene Maraleucel Dosing Regimen

A single target dose of 100 x10^6 CAR-positive T cells (range 50 to 110 × 10^6 CAR positive viable T cells) will be utilized based on the FDA approved product label.

NOTE: Liso-cel manufacturing may result in a product that does not meet all required specifications in order to be released to the patient as commercial liso-cel (also called non-conforming) but considered sufficiently safe and effective to release for treatment of the patient

under an expanded access protocol. Under this circumstance the patient may still be considered eligible after discussion with PI. For the purpose of this protocol, that product would be considered liso-cel.

5.5 Bridging Therapy

Acalabrutinib will be started 2 weeks prior to apheresis and will be discontinued at least 24 hours prior to the initiation of lymphodepleting chemotherapy. Other bridging therapy between leukapheresis and lymphodepleting chemotherapy is allowed at the discretion of the treating investigator. If in the opinion of the treating investigator a patient requires bridging therapy prior to lymphodepleting chemotherapy, other bridging therapy is permitted and must be discontinued at least 14 days prior to lymphodepleting chemotherapy. Corticosteroids and/or radiation therapy may be utilized in combination with acalabrutinib with no dose modifications. If any other alternative bridging therapy is utilized, acalabrutinib must be discontinued prior to any systemic bridging therapy with a minimum washout period of 24 hours. Acalabrutinib will be held throughout bridging therapy and restarted on day +14 following liso-cel infusion as long as there are no significant hematologic toxicities (grade 3 or higher neutropenia or thrombocytopenia) or any grade CRS or neurotoxicity. In the event of ongoing toxicities on day +14, acalabrutinib will not resume until the cytopenia resolves to grade 2 or better, and the CRS and/or neurotoxicity resolves entirely.

5.6 Lymphodepleting Chemotherapy

All patients will preferentially receive lymphodepleting chemotherapy with fludarabine and cyclophosphamide for 3 days prior to liso-cel. Fludarabine and cyclophosphamide is the preference, but if fludarabine is not available due to a shortage, bendamustine can be used instead of fludarabine and cyclophosphamide. Acalabrutinib will be discontinued at least 24 hours prior to the initiation of lymphodepleting chemotherapy. Lymphodepleting chemotherapy will be administered on days -5, -4, and -3 if fludarabine and cyclophosphamide are used, and will be administered on days -4 and -3 if bendamustine is used. Liso-cel will be administered on day 0 (with a +4-day window) if needed) following completion of lymphodepleting chemotherapy. The fludarabine will be dosed at 30 mg/m2 IV daily x 3 days, and cyclophosphamide will be dosed at 300 mg/m2 IV daily x 3 days. Bendamustine will be dosed per institutional guidelines and administered daily x 2 days. All drugs should be administered per institutional standard, including pre-medications, supportive care, and necessary dose reductions for fludarabine and bendamustine. If patients have cellular product that is out of specification, fludarabine should be administered and dose reduced per out of specification protocol. The purpose of this chemotherapy is to induce lymphopenia in order to facilitate engraftment and homeostatic expansion of liso-cel cells.

Liso-cel will be administered per standard institutional routine on day 0 (with a +4-day window).

5.7 General Concomitant Medication and Supportive Care Guidelines

Concomitant Medications and Therapies

All concomitant medications and therapies related to toxicities of CAR T Cell therapy and/or anticoagulation will be recorded in the concomitant medication eCRF.

Excluded Concomitant Medications and Therapies

The following are excluded concomitant medications:

1. Strong CYP3A4 Inhibitors
2. Strong CYP3A4 Inducers

If subject requires a proton pump inhibitor during the course of the study, acalabrutinib can be continued at the current treatment dose. If a subject requires a strong CYP3A4 inhibitor during the course of the study, interrupt use of acalabrutinib. If a subject requires a moderate CYP3A inhibitor reduce dose of acalabrutinib to 100 mg once daily. Avoid concomitant use of strong CYP3A4 inducers. If a subject requires treatment with a strong CYP3A inducer, increase the acalabrutinib dose to 200 mg BID during concomitant administration with the strong inducer and return to recommended dose of 100 mg BID after stopping the strong CYP3A inducer.

Anti-Epileptic Prophylaxis

Anti-epileptic prophylaxis with levetiracetam should be given to all patients with secondary CNS involvement starting on D-1 of CAR T-cell infusion if not on already. In the event that a patient is allergic to or does not tolerate levetiracetam, an alternative antiepileptic agent should be selected.

Infectious prophylaxis

All patients should receive infectious prophylaxis with:

- Acyclovir 400 mg po BID, or equivalent beginning with initiation of lymphodepleting chemotherapy and continuing until the subject's CD4 count exceeds 200 cells per cubic millimeter of blood
- Sulfamethoxazole/trimethoprim SS 1 tab daily, or an alternate PJP regimen at the discretion of the treating investigator (atovaquone, dapsone, pentamidine) beginning with initiation of lymphodepleting chemotherapy and continuing until the subject's CD4 count exceeds 200 cells per cubic millimeter of blood
- It is recommended that patients with prolonged neutropenia > 10 days receive additional prophylaxis including ciprofloxacin 500mg BID or equivalent, and fluconazole 200 mg po QD, unless contraindicated. Use of infectious prophylaxis should take into consideration possible drug-drug interactions with study treatment.
- Pegfilgrastim x1 or G-CSF QD for 7 days beginning on Day 6 is optional.

White blood-cell growth factors: Prophylaxis with G-CSF or pegylated G-CSF is optional starting on Day 6 and for toxicity management as described in the protocol. GM-CSF is contraindicated.

Blood product support

Transfusion support of platelets and packed RBCs may be used at the discretion of the treating investigator. Leukocyte filters are encouraged for all platelet and packed RBC transfusions.

Anti-emetics and Anti-diarrheal agents

Anti-emetics and anti-diarrheals may be administered at the discretion of the investigator. Steroids should NOT be used as an anti-emetic regimen.

Guidelines for the management of Acute Toxicities occurring following the administration of lisocabtagene maraleucel T cells

The management of CRS is discussed in Section 7 and Appendix B. These guidelines are published recommendations based on the observation and management of CRS in other active CAR T programs.

Anti-Cancer Therapy

After receiving liso-cel, subjects should not receive any other therapy that is or may be active against the identified malignancy including other chemotherapies, biologics, radiation therapy or any other investigational agents other than liso-cel and acalabrutinib, which will be given as maintenance therapy before, during and after CAR-T infusion. Localized radiation for symptomatic relief may be allowed after discussion with the principal investigator. The use of bisphosphonates is acceptable at the discretion of the investigator.

Hypogammaglobulinemia

Hypogammaglobulinemic subjects (serum immunoglobulin G [IgG] < 500 mg/dL) should be considered for intravenous immunoglobulin replacement therapy per institutional standard practice.

5.8 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment with acalabrutinib may continue for up to one year after liso-cel infusion or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements

- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.9 Duration of Follow Up

Participants will be followed for AEs, clinical status, and laboratory parameters for up to 24 months after the infusion of liso-cel T cells, or until death, whichever occurs first. After 24 months, patients may be followed for progression and survival. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.10 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Any of the criteria in section 5.8 for taking a participant off protocol therapy
- PI Decision
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

In the case of medical or natural emergencies (i.e., holidays, snowstorms, acute infection) occurring after initiation of chemotherapy, the infusion of liso-cel may be delayed up to one week at the investigator's discretion. Subjects who do not initiate chemotherapy within 12 weeks of enrollment will be withdrawn; however, their liso-cel product can be stored for up to 1 year if feasible if they re-enroll at a later date.

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Guidelines for Management of Toxicities

Event	Management/Next Dose for Acalabrutinib
Grade 4 neutropenia in the absence of fever	**First occurrence:** • Hold acalabrutinib and receive growth factor support per institutional guidelines. Acalabrutinib should be held until neutrophil recovery to grade <=1 or baseline and can be resumed at the same dose level if recovery occurs within 7 days of adequate supportive care • If neutropenia does not resolve to grade 3 or less within 7 days of adequate supportive care, hold acalabrutinib and administer G-CSF or peg-GCSF per institutional routine until neutrophil recovery to grade <=1 or baseline and then resume acalabrutinib at one lower dose level **Subsequent occurrence:** • Hold acalabrutinib and administer G-CSF or peg-GCSF per institutional routine until neutrophil recovery to grade <=1 or baseline and then resume acalabrutinib at one lower dose level • If grade 4 toxicity recurs at the lowest dose level of acalabrutinib, acalabrutinib will be discontinued. Acalabrutinib may be held for toxicity for up to 28 consecutive days. If, in the opinion of the investigator, it is in the patient's best interest to restart acalabrutinib treatment after > 28 days, approval must be obtained from the overall study PI.
Grade 3 or 4 neutropenia with fever	**First occurrence:** • Hold acalabrutinib and administer G-CSF or peg-GCSF per institutional routine until patient is afebrile and has neutrophil recovery to grade <=1 or baseline, and then resume acalabrutinib at one lower dose level • Management of neutropenic fever per institutional routine **Subsequent occurrence:** • Hold acalabrutinib and administer G-CSF or peg-GCSF per institutional routine until patient is afebrile and has neutrophil recovery to grade <=1 or baseline. If toxicity recurs at the lowest dose level of acalabrutinib, permanently discontinue acalabrutinib and administer G-CSF or peg-GCSF per institutional routine. • Management of neutropenic fever per institutional routine Acalabrutinib may be held for toxicity for up to 28 consecutive days. If,

	in the opinion of the investigator, it is in the patient's best interest to restart acalabrutinib treatment after > 28 days, approval must be obtained from the overall study PI.
Grade 4 anemia	• Hold acalabrutinib. • Administer packed RBCs per institutional practice • Evaluate for bleeding as clinically appropriate • For the first occurrence, acalabrutinib may be resumed at full dose upon recovery of toxicity to grade <= 3. • For subsequent occurrences, resume acalabrutinib at one dose level lower upon recovery of toxicity to grade <= 3. • For patients at the lowest dose level of acalabrutinib, acalabrutinib will be discontinued. Acalabrutinib may be held for toxicity for up to 28 consecutive days. If, in the opinion of the investigator, it is in the patient's best interest to restart acalabrutinib treatment after > 28 days, approval must be obtained from the overall study PI.
Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding	• Hold acalabrutinib. • Administer packed RBCs and/or platelets as clinically indicated. • CBC should be repeated every 2-4 days until recovered to grade <= 1 with no bleeding. • For patients with no prior events acalabrutinib may be resumed at full dose • For subsequent occurrences, acalabrutinib should be resumed at one dose level lower. • For patients at the lowest dose level of acalabrutinib, acalabrutinib should be discontinued. Acalabrutinib may be held for toxicity for up to 28 consecutive days. If, in the opinion of the investigator, it is in the patient's best interest to restart acalabrutinib treatment after > 28 days, approval must be obtained from the overall study PI.

Event	**Management/Next Dose for Acalabrutinib**
General guidance for treatment delays and discontinuation	• Acalabrutinib may be held for toxicity for up to 28 consecutive days. If, in the opinion of the investigator, it is in the patient's best interest to restart acalabrutinib treatment after > 28 days, approval must be obtained from the overall study PI.
Grade >=3 Non-Hematologic Toxicity (other than	• For toxicities suspected to be related to acalabrutinib, acalabrutinib will be held until recovery to <= grade 1 or baseline, and then resume at 1 dose level lower.

Event	Management/Next Dose for Acalabrutinib
atrial fibrillation, hypertension, or laboratory values considered not clinically significant)	• For toxicities suspected to be unrelated to acalabrutinib, the acalabrutinib may continue or be held at the discretion of the treating investigator and then resumed at the same dose level if this was the first occurrence. If this was a subsequent occurrence of the same toxicity, the acalabrutinib will be held until <= grade 1 or baseline, and then resumed at one lower dose level. • If the toxicity event recurs at the lowest dose level, acalabrutinib will be discontinued.
Grade >= 3 atrial fibrillation or hypertension	• For grade >= 3 atrial fibrillation or hypertension that is adequately controlled with oral medication, acalabrutinib does not need to be held/reduced. • For patients experiencing atrial fibrillation that is symptomatic or incompletely controlled, the acalabrutinib should be held. Once the atrial fibrillation is adequately controlled, acalabrutinib may be restarted at the original dose for grade 3 atrial fibrillation or 1 dose level lower for grade 4 atrial fibrillation.
Anaphylaxis	• In case of anaphylaxis, acalabrutinib should be permanently discontinued.
New-onset neurologic manifestations suggestive of PML	• Withhold acalabrutinib • Conduct appropriate diagnostic evaluation for PML • If PML is ruled out, resume treatment at current dose. • If PML is confirmed, permanently discontinue study treatment.

BTK inhibitors have been associated with susceptibility to bleeding. Study treatment with acalabrutinib should be held for 3 to 7 days before and after surgery, depending upon the type of surgery and the risk of bleeding.

Acalabrutinib Dose Levels

Level	Dose for Acalabrutinib
0	100 mg BID
-1	100 mg QD

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.2 Adverse Events

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

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.
- 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 and do not require expedited reporting:

- **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. In addition, elective hospitalizations solely for TLS prophylaxis, and without occurrence of TLS or other AE during the hospitalization, also should not be reported as AEs or 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 (e.g., 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 (e.g., 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.

7.2.1 Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest (AESI) are events that may not typically be considered to meet the regulatory criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the timely review of safety data and narrative (may be requested by the FDA or the sponsor-Investigator). It can be, for example, a non-serious non-specific start of an event, which may be an early manifestation of a serious potential risk. An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious. If the Investigator has any questions in regards to an event being an AESI, the Investigator should promptly contact the Sponsor-Investigator.

The same SAE reporting form, assessment and reporting timelines apply to AESIs. For reporting purposes, they need to be treated as if they were serious events even when these events are non-serious and do not meet seriousness criteria. The following events are adverse events of special interest (AESIs) for subjects exposed to acalabrutinib and/or liso-cel, and must be reported to the Sponsor-Investigator expeditiously (see Section 7.4 for reporting instructions), irrespective of regulatory seriousness criteria or causality:

- Ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.)]
- Grade 3 or higher cytokine release syndrome (CRS)
- Grade 3 or higher immune effector cell-associated neurotoxicity syndrome (ICANS)
- Grade 3-4 cytopenias persisting past day 28
- Grade 3 or higher infections
- Grade 3 or higher febrile neutropenia

7.2.2 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 Sponsor-Investigator to applicable regulatory authorities.

An SAE is an AE occurring at any dose that results in one or more of the following:

- Results in death
- Is life-threatening (life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe)

- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may jeopardize the subject or may require intervention to prevent one of the outcomes listed above. Medical and scientific judgement must be exercised in deciding whether other situations must be considered an SAE

In addition to the definition above, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus, or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. AEs for malignant tumors reported during a study should be assessed as an SAE. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual basis should be applied to clarify that the malignant tumor event should be assessed and reported as a Non-Serious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Elevations in liver biochemistry that meet Hy's Law criteria (treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN) are reported as SAEs, using the important medical event serious criterion if no other criteria are applicable.

7.2.3 Severity

Definitions found in the CTCAE version 5.0 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

7.2.4 Adverse Event Reporting Period

All AEs/SAEs should be captured from the date of first dose of acalabrutinib. All AEs/SAEs and Special Situations, irrespective of attribution of causality, must be reported.

AE reporting, irrespective of seriousness, ends 30 days after the last dose of the last study drug, or at documented disease progression, whichever is longer. If patient has not experienced disease progression at 90 days after the last dose of the last study drug, only AEs considered at least possibly related to any study drug(s) must be reported through Year 5 or disease progression, whichever occurs first.

SAEs considered related to study drug(s) or study procedures occurring after the end of the comprehensive AE reporting period (as defined above) must be reported through Year 5 or documented disease progression, whichever occurs first.

If an SAE is present at the last study visit, the SAE 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. Resolution/stable means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the event.

7.2.5 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation timepoints 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.

Each recorded AE or SAE will be described by its diagnostic term, duration (e.g., 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).

7.2.6 Pregnancy

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.

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 [guidance applicable to acalabrutinib monotherapy only]. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

7.2.7 Overdose

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. If the associated AE fulfills serious criteria, the event should be reported to AstraZeneca per contractual guidelines. The Sponsor-Investigator should report any SAEs to the IRB and Regulatory Authorities per institutional and/or regulatory guidelines, and to AstraZeneca 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.

7.2.8 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.

7.3 Expected Toxicities

7.3.1 Expected Toxicities of Acalabrutinib

The following summarizes the experience with acalabrutinib in hematologic cancer studies. Full details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib Investigator Brochure.

Contraindications

No contraindications are known for acalabrutinib.

Important Identified Risks:

- The following summarizes the important identified risks observed with acalabrutinib in hematological cancer studies. Full details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib Investigator's Brochure. **Hemorrhage**

  Serious hemorrhagic events, including fatal events, have occurred in clinical trials with acalabrutinib.

  The mechanism for hemorrhage is not well understood. Patients receiving antithrombotic 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.

- **Infections**

  Serious infections (bacterial, viral, and fungal), including fatal events, have occurred in clinical studies with acalabrutinib. The most frequent 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 (HBV) reactivation, aspergillosis, and progressive multifocal leukoencephalopathy (PML) have occurred.

  Consider prophylaxis in subjects 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.

- **Cytopenias**

  Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Monitor blood counts as specified in the schedule of events and as medically appropriate.

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

- **Second Primary Malignancies**

  Events of second primary malignancies, including non-melanoma skin carcinomas, have been reported in clinical studies with acalabrutinib. The most frequently reported second primary malignancy was skin cancer (basal cell carcinoma).

  Subjects should be monitored for signs and symptoms of malignancy. Subjects who

develop a second primary malignancy should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated, and it may be necessary for subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the Sponsor.

- **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.

  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.
- **Hepatotoxicity**
  This is one important potential risk for acalabrutinib monotherapy. The mechanism underlying etiology is currently unknown. Following a comprehensive review of hepatotoxicity events in the acalabrutinib clinical program, there was insufficient evidence to establish an association between hepatotoxicity events and acalabrutinib due to the contribution of confounding factors, absence of clinical symptoms, and quick recovery without treatment for patients with transaminase elevation. There is limited evidence regarding hepatotoxicity of noninfectious etiology from literature for other BTK inhibitors.

7.3.2 Drug-Drug Interactions of Acalabrutinib

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

However, acalabrutinib is metabolized by CYP3A. Concomitant administration of acalabrutinib with a strong CYP3A and P-glycoprotein (P-gp) inhibitor, itraconazole increased exposure by approximately 5-fold. Conversely, concomitant administration of acalabrutinib with a strong CYP3A inducer, rifampin, decreased acalabrutinib exposure and could reduce efficacy. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A 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 inhibitor while on study, the subject should be monitored closely for any potential toxicities and the dose of acalabrutinib modified as per Section 6.

The effect of agents that reduce gastric acidity (e.g., 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 capsules. Use of omeprazole, esomeprazole, lansoprazole, or any other proton pump inhibitors while taking acalabrutinib capsules 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, and all subjects receiving proton-pump inhibitors should be treated with acalabrutinib tablets.

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 subject should preferentially receive acalabrutinib tablets. If the H2-receptor antagonist must be taken with an acalabrutinib capsule, it should be given approximately 2 hours after an acalabrutinib capsule dose. If treatment with an antiacid is required, separate dosing from acalabrutinib capsule by at least 2 hours.

7.3.3 Reproductive Toxicity

7.3.3.1 Reproductive Toxicity Summaries for Study Drugs

Acalabrutinib

The potential for acalabrutinib to be excreted in breast milk of nursing mothers is unknown.

For results of acalabrutinib nonclinical reproductive toxicity studies, including definitive embryofetal development studies, please refer to the Investigator Brochure.

Women of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib. For male subjects with a pregnant or non-pregnant WOCBP partner, no contraception measures are required. Please refer to the Investigator Brochure for detailed definitions for WOCBP and highly effective methods of contraception.

Subjects should promptly notify the investigator if they, or their partner, become pregnant during this study, or within 2 days after the last dose of acalabrutinib. If a female subject becomes pregnant during the treatment period, she must discontinue acalabrutinib immediately. Pregnancy in a female subject or a male subject's partner must be reported as outlined in Section 7.

7.3.3.2 Definitions for WOCBP and Methods of Contraception

Definitions for WOCBP and for Subjects of Non-Reproductive Potential

WOCBP are women who are fertile following menarche and until becoming postmenopausal unless permanently sterile; permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women are considered to be of non-reproductive potential if they meet any of the following criteria:

- Postmenopausal, defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion, at least 6 weeks before Screening
- Have a congenital or acquired condition that prevents childbearing.

Men are considered to be of non-reproductive potential if they are permanently sterile due to bilateral orchidectomy.

Definition for Highly Effective Methods of Contraception

Highly effective methods of contraception (to be used during heterosexual activity) are defined as methods that can achieve a failure rate of <1% per year when used consistently and correctly. Such methods include:

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

Hormonal contraception may be susceptible to interaction with study or other drugs, which may reduce the efficacy of the contraception method.

Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed during the entire period of risk associated with the study treatments as the subject's preferred and usual lifestyle. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

If a contraceptive method is restricted by local regulations/guidelines, then it does not qualify as an acceptable highly effective method of contraception for subjects participating at sites in the relevant country/region. For male subjects with a pregnant or non-pregnant women of childbearing potential partner, no contraception measures are required.

7.3.4 Expected Toxicities of Lisocabtagene Maraleucel

7.3.4.1 Cytokine Release Syndrome (CRS) and Monitoring

The primary acute toxicity observed to date with CAR T cells has been CRS, and this protocol will follow the recommendations and management for CRS using established consensus guidelines. CRS and neurotoxicity grading will be performed utilizing the 2018 ASBMT consensus criteria.

For this protocol, CRS is defined as a constellation of symptoms which may include (but are not limited to) fever, chills, hypotension, dyspnea, hypoxia, confusion, mental status changes, seizures, myalgias, nausea and vomiting, and laboratory abnormalities including elevated AST, ALT, bilirubin, CRP, D-dimers, PT/INR, ferritin, urea and/or creatinine (see Table 2).

Monitoring for CRS should include a physical exam, vital signs, and lab testing per the clinical trial schedule of events (SOE), unless otherwise clinically indicated, in which case additional clinical assessments or interventions should be performed at the discretion of the investigator.

Any subject with a fever ≥100.4°F within 28 days of liso-cel T cell infusion should have a workup for CRS. The diagnostic work-up of CRS includes an evaluation for an infectious etiology (e.g., blood cultures, urine culture, chest X-ray, as indicated). Clinical laboratory tests include measurements of serum ferritin, C-reactive protein (CRP), comprehensive chemistries, coagulation, and blood counts.

Within the first 28 days following infusion, subjects experiencing a fever ≥ 100.4°F, rapidly rising CRP, altered mental status, unstable vital signs, abnormal laboratory findings, or any other concerning medical conditions should be admitted for monitoring and further workup, at the discretion of the investigator or treating physician.

Treatment of CRS will follow protocol guidelines and may be modified in the future as newer standards become available.

If admitted, subjects should be afebrile for 24 hours with declining inflammatory markers and resolution of any signs or symptoms suggesting of CRS and neurologic toxicity prior to discharge.

Table 2: Clinical Signs and Symptoms Associated with CRS

Organ System	Symptoms
Constitutional	Fever +/- rigors, malaise fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-Dimer, hypofibrinogenemia +/- bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures

Guidelines for the management of toxicities related to liso-cel T cells infusion have been provided in Appendix B. These guidelines are based on available literature for the management of CRS and may need to be adjusted based on the individual clinical circumstances of each subject. The guidelines are not protocol required therapy as they may need to be adjusted but serve to provide a single consistent framework for the evaluation and management of CRS and liso-cel T cells related toxicity to mitigate risk to subject.

7.3.4.2 Temperature Self-Monitoring

Treated subjects must take their temperature every 8 hours from Day 0 through Day 14 post liso-cel T cells infusion and contact their treating investigator for any fever ≥100.4°F through Day 28 post liso-cel T cells infusion. Subjects should not take any nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin, Advil), Naproxen Sodium (Aleve), or acetaminophen (Tylenol) because these can mask fevers. Aspirin should also not be taken unless clinically indicated for another reason such as a cardiac condition. Fevers are a critically important sign that requires subjects to report to the treating institution as soon as possible. Fevers might possibly be the only warning of life-threatening toxicity that can quickly arise in subjects receiving CAR T cells. If subjects are in clinic for a visit when a self-monitoring temperature is to be done the temperature may be taken in the clinic, by clinic staff. At the discretion of individual investigators, subjects may be hospitalized for AE monitoring if preferred.

Subjects are required to stay within a 30-mile radius of the treating institution; subjects should be evaluated and/or admitted to the treating institution due to the institution's familiarity with the treatment protocol and appropriate management of CRS.

7.3.4.3 Neurologic Toxicity

Neurologic toxicity has been reported in anti-CD19 and anti-BCMA CAR T cell clinical trials, including confusion, agitation, obtundation, aphasia, seizures, and myoclonus. To date, the neurologic toxicity has been reversible in a majority of cases however isolated events of fatal neurologic toxicity have been seen in CARs containing a CD28 costimulatory domain [33-36].

Because these syndromes are only now being characterized in the setting of CAR T cell therapy, in the event of neurologic toxicity it is recommended that investigators thoroughly assess and manage subjects for possible etiologies according to institutional guidelines (See Appendix B), which may be modified in the future as more published guidelines become available. Treatment intervention with corticosteroids and/or cyclophosphamide has demonstrated success in other studies[37]. Grading and management of neurotoxicity will be performed as per 2018 Lee criteria[38].

During the post-infusion period, subjects treated on this protocol will be monitored with routine neurocognitive assessments as per the SOE unless otherwise clinically indicated. In the event of suspected neurotoxicity, patients will undergo additional workup which may include a lumbar puncture, EEG, and/or CT/MRI imaging as clinically indicated and in coordination with neuro-oncology as per standard institutional practice. Neurotoxicity will be managed with dexamethasone, anakinra, and/or other agents as per the judgement of the clinical investigator.

7.3.4.4 B cell aplasia and hypo/agammaglobulinemia

Transient or permanent B-cell aplasia with associated hypogammaglobulinemia or agammaglobulinemia is an expected-on target effect of liso-cel therapy in patients with sustained tumor response. This occurs since non-malignant B cells express CD19 and is expected to resolve if and when the liso-cel cells are cleared.

Monitor immunoglobulin levels after treatment with liso-cel. Hypo/agammaglobulinemia is typically managed with immunoglobulin replacement therapy dependent upon age-specific, disease-specific, and local institutional guidelines. Use infection precautions including antibiotic prophylaxis as appropriate and per local standard of care. In general B cell aplasia and hypogammaglobulinemia, of various causes, can be associated with increased rates of infection. Such infections are typically sinopulmonary, but other sites and types of infections have also been reported.

Other potential complications of B cell aplasia include progressive multifocal leukoencephalopathy (PML) and reactivation of hepatitis B virus. Neither PML nor reactivation of hepatitis B virus have been observed to date with liso-cel. However, in other therapies associated with B cell aplasia these complications have been observed.

The safety of immunization with live viral vaccines during or following liso-cel treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of lymphodepleting chemotherapy, during liso-cel treatment, and until immune recovery following treatment with liso-cel.

Pregnant women who have received liso-cel may have hypo/agammaglobulinemia. Immunoglobulin levels should be assessed in newborns of mothers treated with liso-cel.

7.3.4.5 Hypersensitivity Reactions

Hypersensitivity reactions may occur with an infusion of liso-cel. Serious hypersensitivity

reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) in liso-cel. Hypersensitivity prophylaxis should follow institutional standards; however, steroids should not be given.

7.3.4.6 Serious Infections

Serious infections, including life-threatening and fatal infections, occurred in patients after liso-cel infusion. In the TRANSFORM NHL 001 study, infections (grade 3-5) after liso-cel infusion occurred in 12% of patients including 4% with grade ≥ 3 bacterial infections, 1% with grade ≥ 3 fungal infections and 1% with grade ≥ 3 viral infections[21]. Prior to liso-cel infusion, infection prophylaxis should follow guidelines as outlined in Section 5.7 and after treatment the patient should be monitored for signs and symptoms of infection and treated appropriately.

Febrile neutropenia (Grade 3 or 4) was also observed in 9% of patients in TRANSFORM NHL 001. Febrile neutropenia may be concurrent with CRS. In the event of febrile neutropenia, the patient should be evaluated for infection and managed with broad-spectrum antimicrobials, fluids and other supportive care as medically indicated.

7.3.4.7 Cytopenias Not Resolved by Day 28

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and liso-cel infusion. In TRANSFORM NHL 001, Grade 3 and 4 cytopenias not resolved by day 29 following liso-cel treatment occurred in 37% of patients. Among those with prolonged cytopenias, at 90 days following liso-cel, recovery to grade 2 or lower anemia, neutropenia, and thrombocytopenia, respectively, occurred in 82%, 84%, and 62% of patients.

Prolonged neutropenia has been associated with increased risk of infection. G-CSF may be administered per institutional routine and judgement of the treating investigator. GM-CSF is prohibited.

7.3.4.8 Progressive Multifocal Leukoencephalopathy (PML)

PML is rare but well described with antibody therapies causing B cell aplasia[39]. It is a demyelinating disease of the central nervous system, resulting from infection of oligodendrocytes and astrocytes, mostly with JC virus. PML classically has a subacute clinical presentation with focal neurologic deficits, such as weakness, speech difficulties, unsteady gait and hemiparesis. Ophthalmic symptoms are relatively common, occurring as homonymous hemianopia which progresses to cortical blindness. Seizure and headache are uncommon. Dementia, manifesting as deficits in cognition, personality changes, and memory impairment are also common, but rarely occurs in the absence of the focal neurologic deficits of PML. Lesions identified by radiographic assessment are generally confined to the white matter with occipitoparietal lobe lesions without mass effect being most common.

In general, patients with known B cell aplasia are at increased risk for PML. Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. The clinician should evaluate the patient to determine if the

symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a neurologist should be considered as clinically indicated.

7.3.4.9 **Uncontrolled T Cell Proliferation**

Liso-cel transduced cells could theoretically proliferate without the control of normal homeostatic mechanisms. In pre-clinical studies and clinical experience to date anti-CD19 CAR transduced cells have only proliferated in response to physiologic signals or upon exposure to CD19 antigen[40-42]. In the context of liso-cel therapy, it is expected that the T cells will proliferate in response to signals from the CD19 expressing malignant tumor and normal B cells. This could be beneficial or harmful depending on the extent of proliferation.

If uncontrolled T cell proliferation occurs (e.g., expansion of T cells in the absence of CD19 antigen), patients may be treated with corticosteroids such as methylprednisolone (2 mg/kg/d i.v.) or chemotherapy, such as high dose cyclophosphamide. Investigators should further discuss this with Bristol Myers Squibb. Toxicity associated with allogeneic or autologous T cell infusions has been managed with a course of pharmacologic immunosuppression. T cell-associated toxicity has been reported to respond to systemic corticosteroids[43]. This theoretical toxicity is distinct from the toxicity associated with a CRS that develops during T cell proliferation upon exposure to CD19 expressing cells. CRS associated with T cell expansion is managed with anti-cytokine therapy, not immunosuppressants. In an animal model the EGFR antibody cetuximab was used to ablate the EGFRt-expressing CAR T cells in vivo[44]. Currently there is no data available on use of cetuximab or other EGFR-directed antibodies for depletion of liso-cel CAR T cells in humans.

7.4 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.

- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.5 Expedited Reporting Requirements for SAE's and AESI's

This section describes all required expediting reporting.

7.5.1 Expedited Reporting Guidelines to the Sponsor-Investigator:

In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the PI.

Investigators **must** report to the Sponsor-Investigator any serious adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form. All events meeting Adverse Event of Special Interest (AESI) definition as defined in section 7.1.1 and SAE definition as defined in section 7.1.2 should be reported, regardless of attribution.

Investigators should report any SAEs and AESIs to the Sponsor-Investigator within <24 hours or per local regulations using the SAE Reporting Form.

7.5.2 Expedited Reporting Guidelines to the DFCI IRB:

Investigative sites within the DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB AE reporting policy. Only AE's that meet the DFCI IRB's reporting policy are reported to the DFCI IRB. The Sponsor-Investigator must also be notified of all reports submitted to the DFCI IRB.

7.5.3 Expedited Reporting Guidelines to the FDA:

The Sponsor-Investigator will be responsible for all communications with the FDA. The Sponsor-Investigator will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5.4 Expedited Reporting Guidelines to the Funder (AstraZeneca):

The Sponsor-Investigator will notify AstraZeneca in parallel with any submission to the IRB and concerned Regulatory Authority for Suspected Unexpected Serious Adverse Reactions (SUSARs) and within fifteen (15) calendar days of awareness for other SAEs or Special Situation Reports using individual unblinded or blinded case reports (Institution's Standard SAE Report Form, MedWatch, or CIOMS). New information will be submitted to AstraZeneca within the same time frame as initial reports.

Whenever possible, SAEs should be reported by diagnosis term not as a constellation of

symptoms.

Death due to disease progression should be recorded on the appropriate form in the electronic data capture (EDC) system. If the primary cause of death is disease progression, the death due to disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to AstraZeneca Drug Safety, or designee, as outlined above.

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

All SAEs, Pregnancy, Overdose, and other Special Situation reports, Adverse Events of Special Interest and Hy's Law reports are to be submitted to the AstraZeneca Product Safety mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com.

Special situations are other situations of relevance for monitoring the safety of AstraZeneca products and which may or may not be associated with an AE. These special situations must be collected/received, even if no AE occurred:

- Exposure to product during pregnancy (see Section 7.1.6)
- Exposure to product whilst breastfeeding
- Overdose
- Abuse
- Misuse
- Off-label Use
- Medication error
- Occupational exposure
- Lack of efficacy
- Drug interactions
- Unexpected benefit

7.6 Reporting to the NIH Office of Biotechnology Activities (OBA)

The Sponsor-Investigator will be responsible for all communications with the OBA. The Sponsor-Investigator will report to the OBA, regardless of the site of occurrence, any serious adverse event that meets the OBA's criteria for expedited reporting following the reporting requirements and timelines set by the OBA.

7.7 Reporting to the Institutional Biosafety Committee (IBC)

Participating investigators will register and report on research protocols involving biohazards (i.e., recombinant DNA or infectious agents) according to the reporting requirements set by their respective IBC.

7.8 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.9 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.

8.1 Acalabrutinib

8.1.1 Description

The chemical name is: 4-{8-Amino-3-[(2S)-1-(2-butynoyl)-2-pyrrolidinyl]imidazo[1,5-a]pyrazin-1-yl}-N-(2-pyridinyl)benzamide. The molecular formula is C26H23N7O32. The molecular weight is 465.507.

Acalabrutinib is hepatically cleared with a plasma half-life of 1 hour. Drug interaction information is included in Section 7.2.2.

8.1.2 Form, Storage, and Stability

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. 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 tablets for oral administration is supplied as orange, oval, biconvex tablet with 100 mg of acalabrutinib as the active ingredient. Each tablet also contains inactive ingredients: low-

substituted hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The tablet coating consists of copovidone, ferric oxide yellow, ferric oxide red, hypromellose, medium-chain triglycerides, polyethylene glycol 3350, purified water and titanium dioxide.

Acalabrutinib will be provided in white, high-density polyethylene bottles. Acalabrutinib capsules are packaged in white, HDPE bottles and should be stored according to the storage conditions as indicated on the label. Acalabrutinib tablets will be provided in a bottle with a child-resistant closure. The storage condition for acalabrutinib capsules and tablets is below 30°C (86°F).

8.1.3 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.4 Availability

Acalabrutinib is provided under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI.

8.1.5 Administration

Acalabrutinib capsule and tablet are administered BID and 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. Tablets should also be swallowed whole with water, without being chewed, crushed, dissolved or cut. 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. Vomited doses will not be made up.

Guidance on co-administration of acalabrutinib with agents that affect gastric pH is provided in Section 7.2.2.

8.1.6 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.7 Destruction and Return

Investigational medicinal products (IMPs) will either be disposed of at the study site according to the institutional standard operating procedure or be returned to AstraZeneca with the appropriate documentation. The site's method of destroying AstraZeneca-supplied IMPs must be agreed to by the AstraZeneca. The site must obtain written permission from the AstraZeneca before any AstraZeneca-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form. Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on a drug inventory log or equivalent.

8.2 Lisocabtagene maraleucel

Upon release from the manufacturing facility, the cryopreserved liso-cel cell product is shipped to the investigator. Upon receipt of the cryopreserved liso-cel cell product, and inventory must be performed, and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable liso-cel cell product in a given shipment will be documented in the study files. The investigator must notify AstraZenecaof any damaged or unusable liso-cel cell product that was supplied to the investigator's site.

After logging the liso-cel cells, they will be stored safely and properly. Please note the time between product thawing and completion of the infusion should not exceed 30 minutes to maintain maximum product viability. Therefore, to ensure this timeframe, the product should be thawed in close proximity to the patient's bedside. Additionally, after cell thawing the liso-cel cell product should NOT be washed prior to infusion, all contents will be infused. If the liso-cel cell product appears to have a damaged or leaking bag, or otherwise appears to be compromised, it should not be infused, and should be returned to the manufacturing facility. This issue should be documented properly, and the manufacturing facility should be notified on handling of the product.

In rare instances a patient's incoming apheresis or outgoing product may not meet commercial release testing criteria. These cases can either undergo re-collection to attempt manufacturing again, or infusion of the commercially non-conforming product under an expanded access protocol. Patients on this study may receive a non-conforming product and still remain eligible for the protocol, in which case the non-conforming product is considered the same as liso-cel for the purpose of this protocol.

8.2.1 Study drug packaging and labeling

As liso-cel is an FDA approved product, packaging and labeling will follow commercial formatting and documentation.

8.2.2 Drug supply and storage

Liso-cel cell product must be received, handled, and stored safely and properly by designated personnel at the site. Upon receipt, the liso-cel cell product should be stored according to the

instructions specified on the product labels. Personnel receiving, handling, and storing liso-cel cell product must complete REMS or RMP training accordingly.

8.2.3 Study drug disposal and destruction

Liso-cel cell product may require disposal for a variety of reasons, including but not limited to: 1) Mislabeled product; 2) Condition of patient prohibits infusion, and/or 3) Patient refuses infusion. Any unused product and all used infusion supplies, including the infusion bag and tubing, must be disposed of according to local institutional standard operating procedures.

In the event that liso-cel study cell product manufactured by Bristol Myers Squibb was not shipped to the site for infusion, it will be managed per manufacturing facility process. The liso-cel product will either be utilized for research purposes or it will be destroyed.

8.2.4 Administration

Patients will be evaluated per institutional guidelines prior to infusion to ensure that liso-cel infusion is clinically appropriate. Prior to liso-cel preparation, the patient identity must be matched with the patient identifiers on the liso-cel infusion bag. Liso-cel is for autologous use only. Employ universal precautions to avoid potential transmission of infectious diseases when handling the product.

The infusion bag must be inspected for any breaks or cracks prior to thawing. If the bag is compromised, the contents should not be infused, and Bristol Myers Squibb should be called.

The timing of liso-cel thaw and infusion should be coordinated. If more than one bag is being infused for the treatment dose, wait to thaw/infuse the bag until it is determined that the previous bag is safely administered. The infusion time should be confirmed in advance, and the start time for thaw adjusted so that liso-cel is available for infusion when the recipient is ready.

The infusion bag must be placed inside a second, sterile bag in case of a leak and to protect ports from contamination. Liso-cel should be thawed at 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. The bag will be removed from thawing device immediately; and the product bag should not be stored at 37°C. Once thawed and at room temperature (20°C to 25°C), it should be infused within 30 minutes.

Liso-cel should not be washed, spun down, and/or re-suspended in new media prior to infusion. The contents of the thawed infusion bag should be inspected for any visible cell clumps. If visible cell clumps remain, the contents of the bag can be gently mixed. Small clumps of cellular material should disperse with gentle manual mixing. Liso-cel should NOT be infused if clumps are not dispersed, the infusion bag is damaged or leaking, or otherwise appears to be compromised. Call Bristol Myers Squibb.

Liso-cel infusion should be performed using precautions for immunosuppressed patients. Protective isolation should follow institutional standards and policies. Emergency medical equipment should be available during the infusion in case the patient has a significant reaction to

the infusion such as anaphylaxis or severe hypotension.

The site must confirm that two doses of tocilizumab are on site and available for administration prior to liso-cel infusion.

The liso-cel dose will be administered via intravenous (IV) infusion through a latex free i.v. tubing WITHOUT a leukocyte filter (approximately 10 – 20 mL per minute adjusted as appropriate for smaller children and smaller volumes). The volume in the infusion bag ranges from 10-50mL. All contents of the infusion bag should be infused. If more than one bag is being infused for the treatment dose, wait to thaw/infuse the bag until it is determined that the previous bag is safely administered. It is recommended that the infusion should be completed within 30 minutes of thawing the cryopreserved product. The tubing should be primed with saline and the setup should also contain a Y-arm with an attached supplemental saline bag to be used after the initial infusion is completed. This will allow any remaining product left behind within the bag and tubing to be recovered and infused while maintaining a closed tubing system. Cells from all bag(s) should be infused to complete a single dose.

Vital signs (temperature, respiration rate, pulse, pulse oximetry, and blood pressure) will be taken prior to, during and immediately after the infusion and then approximately every 15 minutes for one hour and repeated at 2 hours. If vital signs are unsatisfactory and unstable, continue to monitor the patient until vital sign stabilization.

Liso-cel contains human cells genetically modified with a lentivirus, all used infusion supplies, including the infusion bag and tubing, must be handled and disposed of according to local institutional biosafety standard operating procedures.

Following liso-cel infusion: Should emergency treatment be required in the event of life-threatening hypersensitivity or other acute infusion-related reaction, supportive therapy such as oxygen, bronchodilators, epinephrine, antihistamines, and corticosteroids should be given according to local institutional guidelines. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Patient or patient's caregiver should monitor the patient's temperature every eight hours for the first 14 days post liso-cel infusion. The patient or patient's caregiver should be instructed to call the treating physician promptly with any signs and symptoms of CRS or neurologic toxicities for possible hospitalization.

Patients and their caregivers should plan to stay within 30 miles of the treatment site for at least 4 weeks after liso-cel infusion, unless otherwise indicated by the treating physician.

While patients are admitted, and at each study visit, ICANS assessments will be performed.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.2 Laboratory Correlative Studies

The persistence, biodistribution, and immunologic effects of liso-cel T cells will be evaluated using peripheral blood samples. For molecular studies (Q-PCR), immune phenotyping and

functional assays, peripheral blood will be collected in Lavender top (K2EDTA) tubes. For cytokine analyses peripheral blood samples will be collected in red top (no additive) tubes.

Samples will be collected per the protocol Schedule of Events (see **Section 10.1 Schedule of Events**).

If tumor tissues, bone marrow aspirates, and/or CSF become available as part of routine clinical care, a sample will be collected for research analysis. Tissue samples will be analyzed for the presence of liso-cel T cells by PCR and/or flow cytometry. Peripheral blood samples may also be analyzed for cytokine levels by Luminex technology. Tumor tissue will be analyzed for CD19 expression by immunohistochemistry and/or flow cytometry.

All research samples will be delivered, processed, and frozen as per SOP to the Gill Laboratory at the University of Pennsylvania Health System Center for Cellular Immunotherapies for storage and bulk analyses. Documentation of sample receipt, processing, and storage and primary data from the research analyses will be collected and stored by the processing lab personnel. All research analyses will be performed based on assay-specific SOP using qualified and, if possible, validated assays.

10. STUDY CALENDAR

Evaluations and procedures identified in the Schedule of Events may be performed at unscheduled visits, as clinically indicated, at the Investigator's discretion in consultation with the Sponsor-Investigator.

Study Procedures

The study consists of 1) a screening phase, 2) followed by an intervention/treatment phase consisting of treatment with acalabrutinib and infusion of liso-cel T cells and 3) follow up. Schedule of evaluations and intervention/treatment is included in **Section 10.1.**

10.1 Schedule of Events

Subject Screening and Registration

Subjects willing to participate in the study will provide written informed consent according to Good Clinical Practice (GCP). Written informed consent must be obtained before the conduct of any Screening tests.

Upon signing the informed consent and a manufacturing slot is confirmed, the subject will be registered and assigned a unique subject number. Once a subject number has been assigned, it cannot be reused, and the number stays with the subject even if the subject is subsequently determined to be ineligible for the study.

Leukapheresis must occur ≤42 days after the start of assessments in Screening. Thus, if re-screening is necessary:

- Informed Consent and Demographics need not be repeated
- Only new Medical History and Disease History since previous screening will be collected
- All other assessments in Table 3 for enrollment must be repeated.
- The subject will maintain their originally assigned unique subject number.

Re-screening of assessments during Baseline may be performed at the discretion of the Investigator and Sponsor-Investigator.

Pre-treatment evaluation

The following tests must be performed within 42 days prior to leukapheresis (except where noted):

- Medical history including prior treatment, current medications, and drug allergies.
- Physical exam including vital signs, pulse oximetry, height, weight, and ECOG performance status
- Laboratory studies including CBC with differential, coagulation factors (PT, INR/aPTT, d-dimer and fibrinogen), comprehensive metabolic panel (includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total bilirubin, alkaline phosphatase, AST, ALT, albumin, calcium, magnesium, phosphorus, LDH, uric acid), quantitative immunoglobulins, and inflammatory markers (CRP and ferritin)
- Serum pregnancy test (for females of childbearing potential only)
- Baseline HIV/HCV/HBV serologies (within 90 days)
- 12-lead electrocardiogram (EKG)
- Baseline echocardiogram or MUGA scan (within 90 days).
- PET/CT of chest, abdomen, and pelvis (SOC scans within 60 days prior to leukapheresis may be used if performed subsequent to most recent lymphoma therapy)
- Administration of Functional Assessment of Quality of Life-General (FACT-G)

Additional information regarding subject eligibility for this trial is listed in **Section 3**.

Screen Failures
Subjects are screen failures if:

- they cannot finish assessments for Screening or are ineligible based on those assessments,
- they meet eligibility criteria during Screening but do not undergo leukapheresis

Data collected on Screen Failure subjects will only include:

- Demography
- Eligibility

Note: Subjects who discontinue from the study after leukapheresis but prior to infusion with liso-

cel T cells will be considered withdrawals. All study data collected through the point of withdrawal will be captured for subjects who discontinue early.

Table 3: Schedule of Events (windows for all study procedures are +/- 3 days unless otherwise noted)

Assessment	~ Wk (-) 10 to 6	~ Wk (-) 6 to 4	~ Wk (-) 4	~Week (-) 2 to 1[11]	~ Day (-) 5-3[10]		D 0* (+4d)	D+1*	D+2 (+1d)	D+4 (+1d)	D+7 (+/-2d)	D+10 (+/-2d)	D+14 (+/-3d)	D+21 (+/- 3d)	D+30 (+/-3d)	Monthly to 6 mo. (+/-2 wk)	Quarterly to Year 1 (+/- 1 mo)	Quarterly to Year 2 (+/- 1 mo)	Every 6 Mos for Years 3-5 (+/- 1 mo)[4]
	Screening	Lead-In Phase	Apheresis	Re-Staging	LD Chemo-therapy		Infusion	Post Infusion	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Response Endpoints at 1, 3, 6, 12, 18, and 24 months and Follow - up				Follow up
Clinical Assessments																			
Inform Consent	X																		
Vital signs	X		X		X		X[1]	X	X	X	X	X	X	X	X	X	X	X	X
Recent Med. History, Physical Examination[6]	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X				X		X								X	X	X	X	X
Concomitant Medications	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Disease Staging/ Disease monitoring (PET/CT)/Tumor response assessments[3]	X			X											X	X	X	X	
ECHO/MUGA	X[8]																		
EKG	X																		
Patient monitoring[9]							X	X	X	X	X	X	X	X	X	X	X	X	
AEs/SAEs		X[6]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
ICE/ICANS assessment							X	X	X	X	X	X	X	X	X	X	X	X	
Quality of life assessment[12]	X				X						X				X	X[12]			
Clinical Labs Testing																			
Blood for Serum pregnancy test[2]	X																		
Blood CBC, differential	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Chemistry/Metabolic Panel[7]	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for CD3/CD4/CD8/CD19 FLOW	X						X					X			X	X[5]	X[5]	X[5]	

Assessment	~ Wk (-) 10 to 6	~ Wk (-) 6 to 4	~ Wk (-) 4	~Week (-) 2 to 1[11]	~ Day (-) 5-3[10]		D 0* (+4d)	D+1*	D+2 (+1d)	D+4 (+1d)	D+7 (+/-2d)	D+10 (+/-2d)	D+14 (+/-3d)	D+21 (+/- 3d)	D+30 (+/-3d)	Monthly to 6 mo. (+/-2 wk)	Quarterly to Year 1 (+/- 1 mo)	Quarterly to Year 2 (+/- 1 mo)	Every 6 Mos for Years 3-5 (+/- 1 mo)[4]
	Screening	Lead-In Phase	Apheresis	Re-Staging	LD Chemo-therapy		Infusion	Post Infusion	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Response Endpoints at 1, 3, 6, 12, 18, and 24 months and Follow - up				Follow up
HBV/HCV/HIV serologies[18]	X																		
Coagulation Factors (PT, PTT, INR, fibrinogen, D-dimer)	X						X	X	X	X	X	X	X	X	X	X	X	X	
Quantitative Immunoglobulins	X												X	X	X	X[14]	X[14]	X[14]	
Inflammatory markers (CRP, Ferritin)	X						X	X	X	X	X	X	X	X	X	X	X	X	
Intervention																			
Acalabrutinib[19]		X	X	X									X	X	X	X	X		
Leukapheresis			X																
Lymphodepletion					X														
Lisocabtagene maraleucel infusion							X												
GCSF/peg-GCSF[13]											X[13]								
Translational lab testing peripheral blood mononuclear cells 25 cc (Lavender)[15]																			
PBMC (functional assays, Lisocabtagene maraleucel T cells immunophenotyping, etc.)	X		X		X[16]		X				X				X	X[17]			
Translational lab testing peripheral blood serum 5 cc (Red)[15]																			
Multiplex cytokines	X		X		X[16]		X				X				X	X[17]			

* The Clinical Investigator will review all re-and post-infusion lab results to determine that it is appropriate to proceed with the infusion. Any clinically significant changes in lab results from the prior value will be reviewed by investigators.

1. Vital signs should be taken prior to CAR T cells infusion, once during the infusion, once at the end of infusion, and then approximately every 15 minutes for one hour and repeated at 2 hours.
2. Pregnancy testing – for females of childbearing potential only (not required for women considered to be of non-reproductive potential (see Section 7.2.3.2))
3. Imaging for re-staging timepoint will be done within 4 weeks of infusion. Imaging for tumor response assessments post liso-cel T cell infusion will be done after months 1, 3, 6, 12, 18 and 24. Tumor response assessment is described in Section 11. MRI studies should be performed with perfusion imaging if possible.

4. After completion of the main study protocol (up to 2 years), subjects will be followed with clinical visits and lab work (complete blood count with differential and comprehensive metabolic panel) every 6 months in years 3-5.
5. Blood for CD3/CD4/CD8/CD19 will be taken at 3, 6, 9, 12, 18, 21, and at 24 months. Once the subject's CD4+ T-cell count exceeds 200 cells per cubic millimeter of blood, additional assessments are no longer required.
6. Medical history should be collected prior to beginning therapy with acalabrutinib. Any adverse events will be collected from the day of acalabrutinib initiation.
7. Laboratory studies using comprehensive metabolic panel (includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total bilirubin, alkaline phosphatase, AST, ALT, albumin, calcium, magnesium, phosphorus, LDH, uric acid). (See Section 10.2 for details)
8. Screening echocardiogram or MUGA scan (to be completed within 90 days of leukapheresis).
9. Patient monitoring will occur from Day 0 through Day 7 post liso-cel infusion, excluding weekends and holidays, and should include vital signs every 8 hours if patient is admitted, unless otherwise clinically indicated. After discharge subjects must take their temperature every eight hours through D +14, and contact their treating investigator for any fever ≥100.4° F which will require hospitalization until the subject has been afebrile for 18 hours. Subjects must remain within 30 miles of site for at least 4 weeks after liso-cel infusion, unless otherwise indicated by the treating physician.
10. Vital signs are also required on D-4 and D-3 of lymphodepletion. Medical history, physical exam, ECOG, and concomitant medications are required D-5 only (for subjects taking Bendamustine instead of Fludarabine, these D-5 assessments should take place on D-4). Quality of life assessment is required on D-5 (+/- 3 days). Complete blood count w/ differential, and blood chemistry/ metabolic panel are required on D-5, D-4, and D-3.
11. Re-staging assessments may extend beyond the defined 1-2-week window, including up to the LDC window as clinically indicated.
12. Quality of life measurements will occur at baseline, day-5 (+/- 3 days), day +7 (+/- 3 days), day +30 (+/- 7 days), day +90 (+/- 14 days), and day +180 (+/- 14 days).
13. Pegfilgrastim may optionally be given x1 on Day 6 or GCSF may be optionally administered beginning on Day 6 for 7-10 days.
14. Blood for immunoglobulins will be taken at 6, 12, 18, 24 months post infusion. Immunoglobulins may be collected more frequently at the study-investigator's discretion.
15. In the event of unexpected events, research samples collection may be done as necessary. This should be done at the PI's discretion.
16. PBMC and multiplex cytokines only need to be drawn on D-5 prior to initiation of lymphodepleting chemotherapy.
17. PBMC, and multiplex cytokines to be performed at 3 and 6 months.
18. Serologies include HIV-1/2 Ab, hepatitis B virus core antibody (HBcAb), hepatitis B virus surface antibody (HBsAb), hepatitis B virus surface antigen (HBsAg), and hepatitis C virus (HCV) antibody. Patients who were HBcAb positive at screening with negative HBsAg and HBV DNA PCR should have a quantitative PCR test *monthly* during treatment and *every 12 weeks* for 12 months after the last dose acalabrutinib. Patients who were HCV positive at screening will need a negative PCR test before enrollment.
19. Acalabrutinib is commenced upon enrollment for two weeks prior to apheresis and continued until day -6 unless patient receives bridging therapy. If patient receives bridging, please reference section 5.5. Acalabrutinib may be started less than two weeks or concurrently with apheresis for patients who in the discretion of the treating investigator cannot wait two weeks for apheresis. Acalabrutinib will be held from day -6 until day +14 and be resumed on day +14 provided the patient has no grade 3 or higher neutropenia or thrombocytopenia, nor CRS or neurotoxicity. If grade 3 or higher neutropenia or thrombocytopenia is present, acalabrutinib will be restarted when these resolve to grade ≤ 2 or baseline. If CRS or neurotoxicity is present, then acalabrutinib will be held until resolution.
20. A month is defined as 30 days.

EDC timepoints – clinical assessments and labs will at least be collected at screening and from all timepoints from treatment onward. Intervention will be collected during treatment. Translational labs will not be collected.

10.2 Study Assessments

Tumor cells CD19 Expression and Tumor Burden

Demographics and Medical History

Demographic data includes gender, age, race, and ethnicity.

A complete medical history should include all relevant prior and current medical history, and should also include anti-cancer therapies, including start and end dates of prior therapies, best response, date of progression or relapse, and reason for progression.

Physical Examination and Vital Signs

A physical examination should include assessments of the following body parts/systems: abdomen, extremities, heart, lungs, and neurological. In addition, symptom-directed exams should be performed. Height is to be measured before starting lymphodepleting chemotherapy.

Vital signs include temperature, respiratory rate, heart rate, blood pressure, and SaO2 by pulse oximetry. Vital signs should be taken prior to liso-cel T cells infusion, during and immediately after the infusion and then approximately every 15 minutes for one hour and repeated at 2 hours. If vital signs are unsatisfactory and unstable, continue to monitor the patient until vital sign stabilization.

Echocardiogram or MUGA scan will also be performed.

Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status assessment is to be assessed according to the Schedule of Events.

Laboratory Tests

Clinical Laboratory Tests

Clinical laboratory tests (Table 4) are to be performed by the local laboratory and reviewed by the Investigator or qualified designee (e.g., physician's assistant, nurse practitioner).

Table 4: Clinical Laboratory Tests

Hematology	Serum Chemistry	Coagulation	Enzymes & Liver Studies	Immunology
CBC with differential ferritin fibrinogen	sodium potassium chloride bicarbonate creatinine glucose blood urea nitrogen calcium uric acid phosphate magnesium C-reactive protein	prothrombin time (PT) partial thromboplastin time (PTT) international normalized ratio (INR) fibrinogen d-dimer	AST ALT alkaline phosphatase total bilirubin albumin LDH	Quantitative immunoglobulins CD4+ T-cell lymphocyte count

Abbrev.: CBC: complete blood count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase
CBC includes hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count.

Blood will also be collected for analysis of T cell subsets, including CD4+ and CD8+ cells.

Additional clinical laboratory tests may be performed at the Investigator's discretion.

Additional Eligibility-Determining Laboratory Tests

During Screening, blood samples will be collected for additional eligibility-determining laboratory tests, as follows:

Serology

Screening serology will be evaluated using standard methods. The serology panel should include the following:

- HIV-1/2
- hepatitis B virus core antibody (HBcAb)
- hepatitis B virus surface antibody (HBsAb)
- hepatitis B virus surface antigen (HBsAg)
- hepatitis C virus (HCV) antibody

Blood may also be drawn for additional serology testing if subject has risk factors or clinical evidence of infection with other communicable disease agents or disease.

Serology results within 3 months prior to leukapheresis are acceptable and would not need to be repeated. Additional serology may be performed if required according to country-specific and institutional guidelines.

Serum β-human chorionic gonadotropin pregnancy test

Required for women of child-bearing potential.

Blood, Bone Marrow, Tissue and CSF Analysis for CAR and CD19

CAR+ T cells and CD19+ cells will be quantified in peripheral blood, bone marrow, tumor biopsies and CSF when possible.

Soluble factors/Multiplex Cytokines

Serum will be analyzed for GM-CSF, IL-1β, IL-2, IL-6, IL-8, IFN-γ, IL-10, IL-12p70, IL-15, MCP-1, and TNFα, in addition to other cytokines as identified. Quantification of markers of endothelial activation, including d-dimer, PTT, INR, ANG1, ANG2, gal-3, VWF multimers, may also be examined as exploratory studies.

Blood Collection for Research

Blood will be collected and stored for potential analyses of B cell subtypes, T cell subtypes, and/or markers of T cell exhaustion.

CAR T Cell Phenotyping

Blood will be collected and analyzed for CAR T cell phenotyping, which includes the analysis of CAR T cell subsets and markers of memory, activation, and trafficking.

Gene Expression

Whole blood, bone marrow aspirate or tissue biopsies will be collected and may be analyzed for gene expression per standard SOPs and according to the NIH standards to avoid uncover single nucleotide polymorphisms (SNPs) that are unique to individuals.

Tissue Collection

Blood, Bone Marrow, CSF and Tumor for Future Research

Additional bone marrow and tissue samples may be collected outside the Schedule of Events and is encouraged in the event of unexpected clinical findings such as toxicity or delayed response. These samples, as well as leftover samples from protocol-specified procedures, may be used for biomarker analyses of proteins, DNA, RNA, and other molecules to study aggressive B-cell lymphomas, and/or gene therapy. Such samples may be stored until the samples are exhausted or until the repository is discontinued. The Sponsor-Investigator will be the custodian of the samples in the repository and any unused samples will be destroyed at the Sponsor-Investigator's discretion.

Collection and storage of the samples described above will be subject to discretionary approval from each center's Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and

the subject's specific written consent. Samples will be labeled with a unique identification number that includes no subject identifying information.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect

Efficacy response will be assessed according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" (Cheson, 2014) based on radiographic tumor assessments (see tables below). Subjects will have radiographic disease assessment by PET and/or CT or MRI scans (minimum of chest, neck, abdomen, and pelvis) at baseline and immediately prior to beginning lymphodepleting chemotherapy and approximately 1, 3, 6, 12, 18, and 24 months following treatment or until disease progression. Efficacy assessment will be performed by PET/CT. Once a complete response (CR) has been demonstrated on PET/CT, subsequent imaging may be performed with CT alone at the discretion of the treating investigator.

11.1.1 Response Criteria

11.1.1.1 Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies	PET-CT	Increase FDG uptake
		Nonavid disease	CT	Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, solitary mass, miliary lesions, nodules
		Nonavid disease	CT	>13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, mass
		Nonavid disease	CT	Nodules
CNS	Signs, symptoms		CT	Mass lesion(s)
			MRI	Leptomeningeal infiltration, mass lesions
			CSF assessment	Cytology, flow cytometry
Other (eg, skin, lung, GI	Site dependent		PET-CT[a], biopsy	Lymphoma involvement

tract, bone, bone marrow)				

Abbreviations: CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; MRI = magnetic resonance imaging; PET = positron emission tomography.
a PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

11.1.1.2 Revised Criteria for Response Assessment

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

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

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

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

[a] Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.
Source: Cheson, 2014.

11.1.1.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e., not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions).

11.1.1.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*

CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.2 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is

objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.3 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from registration to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from registration to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from registration to progression, or censored at date of last disease evaluation for those without progression reported.

Duration of response: Duration of response (DOR) is defined as the time from first response to disease progression or death.

Event free survival: Event free survival (EFS) defined as time from registration to death from any cause, disease progression, or starting a new anti-lymphoma therapy, whichever occurs first.

11.1.4 Response Review

Response will be centrally reviewed by the DF/HCC Tumor Imaging Metrics Core (TIMC).

11.2 Other Response Parameters

Rates of bridging therapy: Rates of bridging therapy defined as the percentage of participants requiring any lymphoma-directed therapy other than the investigational therapy in order to control the disease prior to liso-cel infusion.

Health-care related quality of life: Quality of life (QOL) as measured by FACT-G, which has been validated for use in multiple care settings[45]. The FACT-G consists of four subscales assessing well-being across four domains. These self-reported measures possess strong psychometric properties and have been validated for patients with cancer. We will assess patient QOL at baseline, day -5 (+/- 3 days), day +7 (+/- 3 days), day +30 (+/- 7 days), day +90 (+/- 14 days), and day +180 (+/- 14 days) after liso-cel infusion.

ICU admission rates: ICU admission rates defined as the percentage of participants with an ICU admission within 90 days of liso-cel infusion.

Re-hospitalization rates: All cause re-hospitalization rates defined as the percentage of

participants who experience an unplanned hospitalization within 90 days of liso-cel infusion. Planned hospital admissions for a procedure or treatment will be excluded.

Emergency room (ER) visit rates: All cause ER visit rates defined as the percentage of participants who experience an unplanned ER visit within 90 days of liso-cel infusion. Planned ER visits/hospital admissions for a procedure or treatment will be excluded.

Length of stay: Length of stay (LOS) defined as the number of days a participant is hospitalized for liso-cel infusion.

Rates of acalabrutinib discontinuation due to toxicity: Rates of acalabrutinib discontinuation in participants due to acalabrutinib toxicity.

Adverse event rates: The adverse event rates defined as percentage of participants experiencing an adverse event of any grade as graded by CTCAE.

CRS rates: The CRS rate defined as percentage of participants experiencing CRS of any grade and of grade 3 or higher as graded by the ASTCT consensus grading criteria.

ICANS rates: The ICANS rate defined as the percentage of participants experiencing ICANS of any grade and of grade 3 or higher as graded by the 2018 Lee criteria.

Overall response rate, complete response rate, progression-free survival, overall survival rates among different subtypes of lymphoma: The definitions of the response parameters are the same as defined previously but will be examined among different subtypes of lymphoma in the study.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity

and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Sponsor-Investigator and study team.

The DSMC generally reviews each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported across all sites; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This study will be a phase II single arm study with a single stage design to assess the efficacy and safety of acalabrutinib combined with liso-cel for relapsed/refractory aggressive B-cell lymphomas.

Objectives:

Primary

- To estimate the clinical efficacy of acalabrutinib plus liso-cel in adult subjects with relapsed/refractory aggressive B-cell lymphomas.

Secondary

- To investigate other efficacy parameters of the combination of acalabrutinib plus liso-cel
- To assess the safety of the combination of acalabrutinib plus liso-cel
- To characterize the impact of the combination of acalabrutinib plus liso-cel on quality of life and healthcare utilization

Exploratory

- To investigate pharmacokinetics of acalabrutinib plus liso-cel
- To assess the quality of T-cell collections with acalabrutinib therapy using flow cytometry-based phenotyping and transcriptional analysis.
- To compare the efficacy of acalabrutinib plus liso-cel among different types of lymphoma.

Endpoints:

Primary

- Complete response rate (CRR)

Secondary

- Clinical: Overall response rate, progression-free survival, overall survival, duration of response, event free survival, rates of bridging therapy, health-care related quality of life, ICU rates, re-hospitalization rates, ER visit rates, length of stay
- Safety: Rates of acalabrutinib discontinuation due to toxicity, adverse event rates including CRS and ICANS rates

Exploratory

- Immunophenotypic and genomic profile and functional activity of collected T-cells
- Immunophenotypic and genomic profile and functional activity of CAR T-cells after acalabrutinib
- Overall response rate, complete response rate, progression-free survival and overall survival in aggressive B-cell lymphoma subtypes

The study will use a single-arm, single-stage, exact binomial design. The complete response rate (CRR) of at least 73% will be considered promising whereas a CRR of 53% or less will be considered non-promising.

Twenty-seven eligible patients will be enrolled. If 17 or fewer responses are observed, the regimen will be considered non-promising, and the study will be unsuccessful. If at least 18 responses are observed in 27 patients, the study will be considered successful and the regimen worthy of further study.

The study has an overall power and type-I error of 80% and 0.090, respectively. With a total size of 27 patients, the single-stage exact 90% confidence interval for CRR will be no wider than 34%.

13.2 Sample Size, Accrual Rate and Study Duration

The planned sample size is 27 eligible patients. A total of 27 evaluable participants will be accrued within approximately one year. Up to two additional years of follow-up will be required on the last participant accrued to observe the participants response and toxicity, for a total study duration of 5 years. Patients will continue to be followed for up to 15 years for survival.

13.3 Analysis of Primary Endpoints

All patients who receive liso-cel and undergo response assessment will be considered evaluable for efficacy. CRR is based on the best overall response post-lisocabtagene maraleucel infusion. The CRR is defined as the proportion of subjects achieving an objective response of complete response (CR) according to the Lugano Classification, prior to start of another non-study anticancer therapy. Subjects who received liso-cel with unknown or missing response will be counted as non-responder in the analysis. The combination of acalabrutinib plus liso-cel will be considered to have sufficient efficacy to warrant further testing in this population if 18 or more of the 27 patients achieve an objective response of CR.

13.4 Analysis of Secondary Endpoints

PFS will be summarized using Kaplan-Meier estimates. OS will be summarized using Kaplan-Meier estimates. Data from surviving subjects will be censored at the last time that the subject is known to be alive. DOR will be summarized using Kaplan-Meier estimates. EFS, rates of bridging therapy, QOL, ICU rates, re-hospitalization rates, length of stay, rates of acalabrutinib discontinuation due to toxicity, rates of adverse events, rates of CRS, rates of ICANS, and efficacy parameters among different subtypes of lymphoma will all be reported with descriptive statistics. Summary statistics will be calculated (median, mean, range for continuous variables; frequency and percentage for discrete variables). Time to event outcomes will be estimated using Kaplan Meier method or cumulative incidence curves. Only patients who are infused will be analyzed in subsequent data analysis. Additional exploratory analyses will be primarily descriptive, with results presented graphically and/or as summary statistics.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All participants will be evaluable for any drug related toxicity from the time of their first treatment. Adverse events (AEs) will be coded using CTCAE criteria. All subjects who initiate any study procedures will be included in the assessment of safety. Subject incidence rates of AEs, including SAEs, fatal and treatment related AEs will be reported through the conduct of the study. Changes in clinical laboratory test results, vital signs and physical examination findings will be summarized with descriptive statistics as appropriate. Laboratory parameters will be summarized for changes across study by using descriptive statistics including shifts relative to CTCAE criteria for laboratory abnormalities. Laboratory measures will also be compared with their corresponding normal ranges and the incidence of abnormally high and abnormally low laboratory values will be calculated for each relevant protocol-specified laboratory test. Laboratory values that are of Grade 3 severity or greater will be tabulated by dose and listed on an individual subject basis.

An interim global safety analysis will also be performed after the first 10 patients are enrolled. After 10 patients are enrolled, we will pause enrollment until all 10 have reached day +28. We will then have a global safety analysis including stopping rules for toxicities of special interest, including the detection of prolonged grade 3 or higher neutropenia or thrombocytopenia in 5 or more patients, the detection of grade 3 or higher cytokine release syndrome in 3 or more patients, or the detection of immune effector cell-associated neurotoxicity syndrome in 3 or more patients.

All treated subjects will be followed for overall survival for up approximately 15 years after T cell infusion.

13.5.2 Evaluation of the Primary Efficacy Endpoint

All eligible participants who receive liso-cel and acalabrutinib and who undergo response assessment will be evaluable for efficacy. Subjects who do not undergo response assessment due to clinical progression of disease will also be considered evaluable. Subanalyses will be

performed on the subset of participants who receive liso-cel infusion.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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 B CYTOKINE RELEASE SYNDROME (CRS) AND NEUROTOXICITY MANAGEMENT

Monitoring and Management of late reactions following immune effector cell infusion

Monitoring: Patients will be assessed at a minimum of every 8 hours for signs and symptoms of CRS and graded per modified Lee criteria described in table 5. The following labs will be performed at least daily: CBC w/diff, CMP, Phos, LDH, PT/INR, PTT, fibrinogen, d-dimer, CRP, ferritin, and with increased frequency as clinically indicated

Management: In the event that toxicity is suspected, patients will be placed on continuous telemetry including continuous O_2 monitoring. Vital checks will be assessed at an increased frequency as clinically indicated and supportive measures including fluid management, respiratory support, and vasopressors/inotropic support will be provided. Patients with rapid clinical decline, extensive comorbidities, or older age, will be evaluated by ICU triage. Patients with fevers/febrile neutropenia will be treated as septic/febrile neutropenia with broad spectrum antibiotics. Specific infectious prophylaxis will also be started at time of lymphodepletion per clinical discretion until resolution of symptoms. Patients with neurologic toxicity will be managed per flowchart 1.

Pharmacologic therapy may include:

1. Anti-IL6 therapy can be administered as clinically indicated per table 6.
2. Corticosteroids can be administered as clinically indicated per table 6 and table 10.
3. Low and high dose vasopressor support as clinically indicated.
4. Antiepileptic drugs to include Keppra or another appropriate antiepileptic agent at first sign of CRS/neurotoxicity, with Keppra starting dose of 500mg BID, additional recommendations per neuro-oncology immune effector toxicity management.

Table 5. CRS Grading System – ASBMT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever†	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or‡				
Hypoxia	None	Requiring low-flow nasal cannula^ or blow-by	Requiring high-flow nasal cannula^, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

CPAP: Continuous positive airway pressure; BiPAP: Bilevel positive airway pressure
† Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
‡ CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring one vasopressor and hypoxia requiring low-flow nasal cannula is classified as having Grade 3 CRS.
#Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.
^ Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 liters/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 liters/minute.

Table 6. Management of CRS by Grade

CRS Grade	Anti-IL-6 Therapy	Corticosteroids	Additional Supportive Care
Grade 1	For prolonged CRS (>3 days) in patients with significant symptoms and/or	N/A	• Empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor (G-CSF) if

	comorbidities, consider tocilizumab as per Grade 2		neutropenic and concern for infectious etiology • Maintenance IV fluids for hydration • Symptomatic management of organ toxicities
Grade 2	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total	For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy: Dexamethasone 10 mg IV every 6-12 hours (or equivalent)	• IV fluid bolus as needed • For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to intensive care unit (ICU), consider echocardiogram, and initiate other methods of hemodynamic monitoring • Manage per Grade 3 if no improvement within 24 hours after starting anti-IL-6 therapy • Symptomatic management of organ toxicities
Grade 3	Anti-IL-6 therapy as per Grade 2 if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6-12 hours (or equivalent). If refractory, manage as grade 4	• Transfer to ICU as clinically warranted, obtain echocardiogram, and perform hemodynamic monitoring • Supplemental oxygen including high-flow oxygen delivery and noninvasive positive pressure ventilation • IV fluid bolus and vasopressors as needed. • Symptomatic management of organ toxicities
Grade 4	Anti-IL-6 therapy as per Grade 2 if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours (or equivalent). If refractory, consider methylprednisolone 1000 mg/day IV	• ICU care and hemodynamic monitoring • Mechanical ventilation as needed • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities

Table 7. Anti-IL6 Therapy and Dosing Recommendations

DRUG	RECOMMENDED DOSE FOR CRS AND/OR NEUROTOXICITY	MAXIMUM DOSE	MECHANISM OF ACTION	COMMENTS

TOCILIZUMAB	8 mg/kg IV for up to three doses in a 24-hour period (Maximum 4 doses total)	Maximum 800 mg per dose	IL-6 receptor antagonist	First line agent Doses can be given 8 hours apart

Table 8. Grading of Neurotoxicity (Lee et al. 2018[38])

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score^	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness❖	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor findings§	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP / Cerebral edema	N/A	N/A	Focal/local edema on neuroimaging#	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

‡ ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause. For example, a patient with an ICE score of 3 who has a generalized seizure is classified as having Grade 3 ICANS.
^A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is awake with global aphasia. But a patient with an ICE score of 0 may be classified as having Grade 4 ICANS if the patient is unarousable.
❖Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication)
§ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0 but they do not influence ICANS grading.

Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.
ICE: Immune effector Cell-associated Encephalopathy; ICP: Intracranial pressure; EEG: electroencephalogram.

Table 9. Encephalopathy assessment tools for grading of Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS).

Immune effector Cell-associated Encephalopathy (ICE)
• **Orientation:** Orientation to year, month, city, hospital: 4 points • **Naming:** Name 3 objects (e.g., point to clock, pen, button): 3 points • **Following commands:** (e.g., Show me 2 fingers or Close your eyes and stick out your tongue): 1 point • **Writing:** Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point • **Attention:** Count backwards from 100 by ten: 1 point

Score 10: No impairment
Score 7-9: Grade 1 ICANS
Score 3-6: Grade 2 ICANS
Score 0-2: Grade 3 ICANS
Score 0 due to patient unarousable and unable to perform ICE assessment: Grade 4 ICANS

Table 10. Management of ICANS

Treatment by Grade	
Grade 1	• Supportive care
Grade 2	• Supportive care • Dexamethasone 10 mg IV x 1. Can repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 h if symptoms worsen.
Grade 3	• ICU care is recommended. • Dexamethasone, 10 mg IV every 6 h • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity.
Grade 4	• ICU care, consider mechanical ventilation for airway protection. • High-dose corticosteroids, methylprednisolone 1000 mg/day IV x3 days • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.