PROTOCOL TITLE: Duvelisib Exposure to Enhance Immune Profiles of T Cells in Patients with Diffuse Large B Cell Lymphoma (DEEP T CELLS)

WINSHIP PROTOCOL #: Winship5085-20

COORDINATING CENTER: Winship Cancer Institute, Emory University

PRINCIPAL INVESTIGATOR: Edmund K. Waller, MD/PhD
Professor, Department of Hematology/Medical Oncology
Winship Cancer Institute, Emory University
1365 Clifton Road, B5119
Atlanta, GA 30322
404-727-4995
ewaller@emory.edu

CO-INVESTIGATORS: Sanjay Chandrasekaran, MD
Hematology/Medical Oncology Fellow
Winship Cancer Institute,
Emory University
1365 Clifton Road
Atlanta, GA 30322
253-670-1741
schandrasekaran@emory.edu

Aseala Abousaud, PharmD
Winship Cancer Institute,
Emory University
1365 Clifton Road,
Atlanta, GA 30322
Aseala.abousaud@emoryhealthcare.org

C. Ronnie Funk, MD
Internal Medicine Resident
Winship Cancer Institute,
Emory University
1365 Clifton Road
Atlanta, GA 30322
Ronnie.Funk@emory.edu

STATISTICIAN: Yuan Liu, PhD
Research Assistant Professor
Department of Biostatistics and Bioinformatics
Emory University
1518 Clifton Rd. Atlanta GA 30322
Yliu31@emory.edu

VERSION: Version 22; 04/25/2023

FUNDING SOURCE: Funding will be covered by Secura Bio and Novartis.

INVESTIGATIONAL PRODUCT (IP): Duvelisb; Secura Bio
OTHER AGENT(S): Chimeric Antigen Receptor T Cells; Novartis

☒ **Study Exempt from IND Requirements per 21 CFR 312.2(b).**

REVISION HISTORY (From v19 2/23/21 to v21 6/14/2022)

#	Section	Page(s)	Description of Changes
1	1.2	8	Schema Clarified Duvelisib D0 vs CAR-T Days 0-90
2	1.3	9	Clarified CAR-T Day 0 as cD0
3	2.0	10	Clarified as "duvelisib consumed as documented by the patient"
4	3.0	11	Edit: cannot be downregulated on "*normal*" B cells.
5	4.2.1	18	Clarified language re: missed doses
6	5.3	19	Clarified stopping rules re: significant toxicities
7	5.3	19	Clarified no allowance for dose interruptions
8	5.6	20	Clarified COVID PCR testing rules and negative testing
9	5.7	21	Defined severe non-compliance
10	11.1	29	Re: Sterilization – added salpingectomy
11	12	30	Clarified # to consent vs enroll at primary and sub-site
12	17.5.2	34	Clarified # doses to meet primary endpoint >/= to 75%
13	18.4	39	Added Secura email contact, changed Novartis to cell manufacturer
14	18.4	40	Duvelisib related SAE contact info for Secura for reporting
15	20.0	44	Clarified roles of sponsor vs supporter vs cell manufacturer
16	21.0	45	Edit: if so by whom (eg: sponsor, "*supporter*," subject …
17	11.2	29	Updated exclusion criteria with word "known"
18	1.1, 3.1, 3.2, 5.1, 11.1, 13	7,8,12,15, 16, 29, 31	Include relapsed/refractory follicular lymphoma eligible to receive commercial tisagenlecleucel as part of the eligibility criteria
19	1.3	10	Change window for day 15 assessment to ± 2 days
20	1.3	10	Change window for assessment post-CART to ± 2 days
21	1.1,2, 3.2, 5.1	7, 8, 15, 20	Change duration of duvelisib exposure from 2 weeks to 8-15 days Removed University of Chicago as a site

Table of Contents

1. Study Summary

1.1 Synopsis

This pilot study will evaluate a 8 to 15 day exposure to duvelisib in patients with relapsed/refractory Diffuse Large B Cell Lymphoma (DLBCL) or follicular lymphoma prior to undergoing apheresis of a mononuclear cell product for the purpose of CAR-T manufacturing. The primary objective of the study is to determine whether the immune profile of T cells can be favorably changed by short-term exposure to duvelisib prior to collection of mononuclear cells for CAR-T 19 cell manufacturing. Secondary objectives include feasibility of adherence to duvelisib for 8 to 15 day, assessment of manufacturing time of patients, assessment of proportions of CD27/CD28 T cells and CD4/CD8 double negative Gamma Delta T cells to historical controls, comparison of rates cytokine release syndrome (CRS)neurotoxicity or ICU transfer and overall response rate (ORR) at 90 days. The study will also determine if a 8 to 15 day exposure to duvelisib is safe and well tolerated in this setting.

Title:	Duvelisib Exposure to Enhance Immune Profiles of T Cells in Patients with Diffuse Large B Cell Lymphoma (DEEP T CELLS)
Study Description:	This Pilot study will evaluate whether an 8 to 15 day exposure to Duvelisib will favorably change the immune profile of T cells prior to CAR-T 19 cell manufacturing. We hypothesize that short term exposure to Duvelisib will: • increase frequencies of CD27/28 double positive naïve and memory T cells. • increase frequencies of CD8+CD45RO-CD27+ T cells. • increase frequencies of CD4/CD8 double negative Gamma Delta T cells.
Objectives:	**Primary Objective:** • To assess changes in T cell phenotype after 8 to 15 day exposure to duvelisib prior to collection of mononuclear cells for CAR-T cell manufacturing. **Secondary Objectives:** • To evaluate compliance with duvelisib • To evaluate the CAR-T 19 manufacturing time • To describe frequencies of CD27/28 double positive T cells and CD4/8 double negative T cells • To evaluate expansion and persistence of CAR-T cells • To evaluate overall response rates following CAR-T cell therapy • To evaluate survival rates following CAR-T cell therapy • To describe the frequency of CRS and neurotoxicity requiring ICU transfer (for CRS or neurotoxicity) and/or treatment • Describe the safety and tolerability profile of duvelisib

Endpoints:	**Primary Endpoint:** • The fold increase in the proportion of T cell phenotypes expressing CD 27/28 (to overall T cell count) after 8 to 15 day exposure to duvelisib **Secondary Endpoints:** • The proportion of duvelisib consumed as evaluated by the patient pill diaries. • Manufacturing time of CAR-T 19 cells in weeks (includes manufacturing failure) • The proportion of CD27/28 double positive T cells and CD4/8 double negative T cells • CAR-T kinetics assessment by PCR • Overall response at 90 days after CAR-T cell infusion defined by the Tumor Response Assessment that are complete responders (CR) and partial responders (PR). • Progression-free Survival (PFS) at 90 days per RECIST 1.1 and Overall Survival at 90 days • ICU transfer due to CRS and/or neurotoxicity or due to the treatment with tocilizumab and/or corticosteroids • Grade III-V toxicities (as defined by CTCAE version 5.0)
Study Population:	20 patients will be enrolled with relapsed/refractory DLBCL or relapsed/refractory follicular lymphoma
Phase:	Pilot
Description of Sites/Facilities Enrolling Participants:	This study will be at Winship Cancer Institute, Emory University.
Description of Study Intervention:	Duvelisib is an oral PI3K inhibitor that is given at a dose of 25mg BID prior to manufacturing of CAR-T cells.
Study Duration:	We estimate that the duration of the study will be approximately 18 months.

1.2 Schema

Days -14 to 0 Screening

- Total n= 20
- Obtain informed consent
- Screen potential participants by inclusion and exclusion criteria
- Obtain history, document

Day 1 Follow-up assessments of study endpoints and safety
Baseline assessments/ Study Intervention

- Administer initial dose of Duvelisib

Refer to **Section 1.3, Schedule of Activities**

Day 8

- Refer to **Section 1.3, Schedule of Activities**

Day 15

- Refer to **Section 1.3, Schedule of Activities**

CART-T Day 0-90 Post CAR-T 19 Infusion Assessments

- Refer to **Section 1.3, Schedule of Activities**

1.3 Schedule of Assessments

Table 1: Pre and During Study Assessments on duvelisib (Day 1= First day of duvelisib)

Procedures and Tests	Days -14 to 0	Day 8 +/-1	Day 15 +/-2
Medical History	X		
Physical Exam	X	X	X
Performance Status	X	X	X
Vital Signs	X	X	X
Labs:*	X	X	X
CBC	X	X	X
CMP	X	X	X
TSH	X		
Magnesium	X		
Phosphorous	X	X	X
HIV Ag/Ab	X		
Hepatitis Serologies	X		
Covid-19 PCR (-7 to 0)	X		
EKG	X		
Immunophenotyping of T-Cells	X		X
PET/CT*	X		
Serum or Urine Pregnancy Test**	X		
Adverse Events		X	X

* Standard-of-care

** Standard-of-care. Also see section 11.1 regarding risk to fetus and requirement for contraception while on study

Table 2: Post CAR-T 19 Cell Infusion Assessments (post-hospital discharge, will be captured with chart review) (CAR-T Day 0 (cD0)= Date of CAR-T infusion)

Procedures and Tests	Day 7 +/-1 (post CAR-T)	Day 14 +/-2 (post CAR-T)	Day 28 +/-2 (post CAR-T)	Day 42 +/-3 (post CAR-T)	Day 90 +/-3 (post CAR-T)
CAR-T 19 PCR*	X	X	X	X	X
Immunophenotype of CAR-T*	X	X	X	X	X
PET/CT or CT*					X

* Standard-of-care

2. Objectives (and Endpoints)

OBJECTIVES	ENDPOINTS
Primary	
1. To assess the increase in CD27+/CD28+ T cells, after 8 to 15 day exposure duvelisib prior to collection of mononuclear cells for CAR-T cell manufacturing.	1. The fold change increase in proportion of T cell phenotypes co-expressing CD27/28 using multiparametric flow cytometry.
Secondary	
1. To evaluate patient compliance with duvelisib. 2. To evaluate the time required for manufacturing CAR-T using mononuclear cells from duvelisib-treated patients. 3. To describe the frequencies of CD27/28 double positive T cells and CD4/8 double negative T cells 4. To evaluate expansion and persistence of CAR-T cells 5. To evaluate overall response rates following CAR-T cell therapy 6. To evaluate survival rates following CAR-T cell therapy 7. To describe the frequency of CRS and neurotoxicity requiring ICU transfer (for CRS or neurotoxicity) and/or treatment 8. Describe the safety and tolerability profile of duvelisib	1. The proportion of duvelisib consumed as documented by the patient on the pill diaries. 2. Manufacturing time of CAR-T 19 cells in weeks (includes manufacturing failure) 3. The proportion of CD27/28 double positive T cells and CD4/8 double negative T cells 4. CAR-T kinetics assessment by PCR 5. Overall response (per iRECIST) at 90 days after CAR-T cell infusion defined by the Tumor Response Assessment that are complete responders (CR) and partial responders (PR). 6. Progression-free Survival (PFS) at 90 days per RECIST 1.1 and Overall Survival at 90 days 7. ICU transfer due to CRS and/or neurotoxicity or due to the treatment with tocilizumab and/or corticosteroids 8. Grade III-V toxicities (as defined by CTCAE version

3. Background

Diffuse Large B Cell Lymphoma (DLBCL) and relapsed/refractory follicular lymphoma:

Lymphoma is a group of blood cell tumors that arise from the lymphatic systems and can be separated into two categories: Non-Hodgkin Lymphoma (NHL) and Hodgkin Lymphoma (HL). NHL accounts for about 4% of all cancers with an estimated 74,000 new cases diagnosed in 2018.[1] There will be an estimated 20,000 deaths from NHL, which accounts for 3% of all cancer deaths. Diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL) are the most common NHL, accounting for nearly 65% of cases.[2] Standard treatment for DLBCL is a rituximab based regimen in combination with cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone (R-CHOP or R-EPOCH).[3] The five year overall survival (OS) for DLBCL is 62% in the United States and for localized DLBCL, the OS is even more impressive at over 80%.[4,5] Despite the favorable outcomes with DLBCL, one third of patients will have relapsed or refractory disease.[2] These patients are treated with salvage chemotherapy and consolidation treatment with autologous stem cell transplant (ASCT). Unfortunately, about 50% of those patients that receive ASCT will ultimately relapse, and further treatment options become severely limited with a median OS of 6.2 months.[4]

Recently, a novel immunotherapy that manufactures T cells to express the chimeric antigen receptor (CAR-T cells) against CD19, that is pan-expressed on B cells, has been shown to have high response rates in relapsed/refractory B cell cancers including those that have previously received an ASCT.[6] CAR-T cells provide a promising new treatment for heavily pre-treated patients with B cell malignancies, however, there are a sub-group of patients who are unable to manufacture a sufficient amount of CAR-T cells, have poor expansion of CAR-T cells in vivo, or lose persistence of their CAR-T cells post infusion. Thus, better manufacturing of T cells to make them more potent with longer duration are critical to enhancing the success of CAR-T cells.

Chimeric Antigen Receptor T (CAR-T) Cells:

Chimeric antigen receptor (CAR) T cells are genetically engineered T cells that recognize specific tumor antigens.[7] The genes encoding for the CAR are inserted into the T cells using a viral vector with RNA genetic material that is then reverse transcribed into the T cells DNA.[8] The CAR is then transcribed and translated and then expressed on the cell surface where it is able to recognize tumor antigens. There are two components of the CAR including the antigen-recognition domain and the T cell signaling domain. In earlier generations of CARs, the T cell signaling domain only contained an intracellular activation domain. Newer generations have added a single co-stimulatory domain (CD28 or 4-1BB) or two co-stimulatory domains (See Figure 1). For B cell malignancies, including acute lymphoblastic leukemia (ALL) and DLBCL, the most common antigen used for CAR-T cells manufacturing is CD19. CD19 is pan-expressed on B cells and cannot be downregulated on normal B cells. Numerous single center and multi-center studies have been published about CD19 CAR-T cells against NHL and has shown an overall response rate (ORR) ranging from 71%-100%.[7]

Remissions of hematologic malignancy with CAR T cell therapy are associated with one of two profiles of CAR T cell expansion kinetics. Some trials positively associate the ratio of peak CAR T to tumor cells with remission, whereas the bulk of trials associate long-term persistence of CAR T with continued remission. In support of the latter mechanism, expansion and persistence of a single clone (defined by CAR insertion site) comprising 94% of the total CAR T cells was sufficient to induce remission. In study of 41 patients who received CAR T cell therapy to treat CLL, Fraietta et al associated the frequency of CD8+CD27+CD45RO- T cells prior to CAR T manufacture with

remission.[9] These clinical observations suggest CAR T cell phenotype, such as expression of CD27 and CD28, influences response to therapy.

Figure 1: Chimeric antigen receptor (CAR) structures.

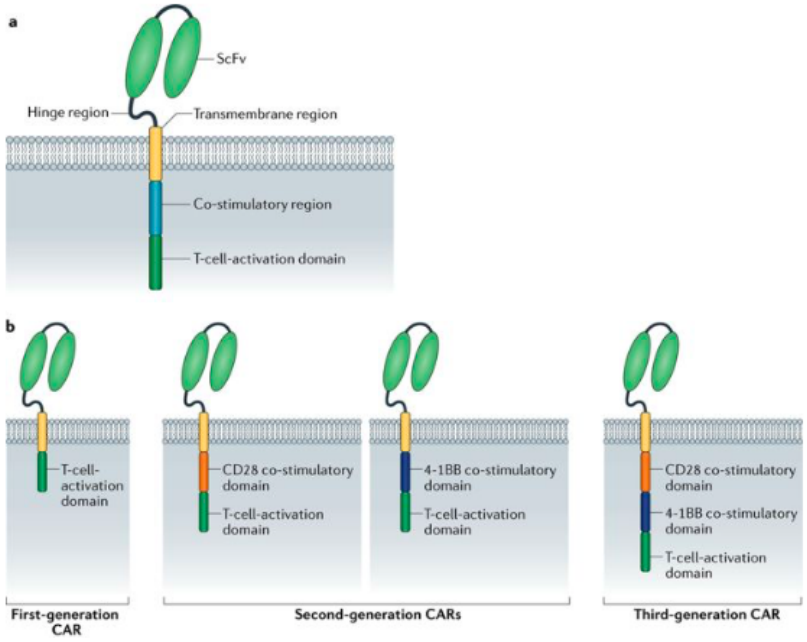


Figure 1: Structure of CAR-T cells (Brudno & Kochenderfer)

Phosphoinositide 3-Kinase (PI3K)

PI3K proteins are divided into three classes of which only Class IA PI3K molecules have been implicated in human cancers, prompting development of isoform-selective inhibitors to Class IA PI3K.[10] Analysis of evolutionary conservation across known class I PI3K signaling cascades reveals the greatest conservation in signaling along the insulin/IGF-1/AKT pathway, suggesting PI3K primarily evolved to regulate cellular proliferation and metabolic changes in response to glucose.[11]

PI3Ks are involved in the generation of lipid second messengers and contain eight catalytic subunits of PI3K, with the P110 gamma and the P110 delta subunits being expressed at much higher levels in immune cells.[12,13] The PI3K p110 subunits work by phosphorylating phosphatidylinositol 4,5 bisphosphate (PIP2) into phosphatidylinositol 3, 4,5 triphosphate (PIP3), which enables anchorage and association of cytosolic proteins near the lipid bilayer, enabling complex signal transduction cascades to occur.[10] In the case of T cells, metabolism of glucose is closely linked to the replicative capacity of the cells, with T cells capable of oxidative phosphorylation exhibiting enhanced replicative capacity whereas T cells that rely upon glycolysis exhibit reduced replicative potential, as reviewed by Van der Windt et al 2013.[14]

PIP3 then goes on to function as a second messenger that initiates multiple signaling cascades, including the phosphorylation of AKT, a serine/threonine protein kinase, leading to downstream

survival and differentiation signals such as mechanistic target of rapamycin 1 (mTOR).[15,16] mTOR, also a serine/threonine kinase, is regulated by amino acids and glucose levels. Upon T cell activation, there is an increase in uptake of amino acids and glucose leading to activation of mTOR1 and this activation is required to maintain the T cell effector functions. [17-20] Activation of mTOR1 also promotes induction of aerobic glycolysis, as well as assistance in maintaining it, which leads to increased differentiation and effector functions, which are shown to be less efficacious in terms of adoptive T cell therapies.[20] By inhibiting mTOR through inhibition of PI3K. PI3K inhibitors promotes memory T cell phenotype by inhibiting aerobic glycolysis and preventing terminal differentiation.[20] One PI3K inhibitor, Idelalisib, inhibits only the delta catalytic subunit, which blocks lymphocyte function.[11] Duvelisib, another PI3K inhibitor, demonstrates inhibition of both PI3K-delta and gamma, but is much more selective for the delta than the gamma isoform of PI3K.[15] [15] Indeed, using whole blood assays, duvelisib achieves inhibition of PI3K delta and gamma at clinically feasible doses (Pachter and Weaver, SITC 2008), which may be important for modulating ratios of CD8:CD4 T cells (Funk et al., SITC 2019; unpublished data, Waller Lab). By targeting either PI3K delta alone or both PI3K delta and gamma catalytic subunits, that are predominantly expressed on immune cells, PI3K inhibitors lead to partial blockade of terminal differentiation of T cells.

T cells and Cancer Immunotherapy

T cells can be categorized based upon whether their T cell receptor (TCR) recognizes antigen by major histocompatibility complex (MHC) in an independent or dependent manner. Alpha Beta T cells contain a TCR that recognize peptide presented by class I or II MHC, whereas Gamma Delta T cells recognize antigens independent of MHC. Gamma Delta T cells are a small and unique population of T cells that compromise less than 5% of the total T cell population.[21] They generally do not express CD4 or CD8 and have the unique role of serving as both effector T cells and initiating and maintaining adaptive immune responses.[22] Gamma-Delta T cells are able to secrete cytokines, including IL-4 and TNFa, that can directly attack and kill tumor cells. They can also act as antigen presenting cells (APCs) and have the capacity to induce CD4+ and CD8+ antigen specific T cells.[23] Pre-clinical studies have shown that gamma delta CAR-T cells have a more naïve T cell phenotype and that their cytotoxicity was equivalent to alpha beta CAR-T cells.[24]

Alpha Beta(+) TCR T cells are the predominant T cells compromising >95% of T cells and can be further sub-categorized into helper, cytotoxic, memory or regulatory T cells.[23] Naïve T cells are antigen inexperienced and are characterized by the expression of CD45RA, CD62L and the co-stimulatory molecules CD27 and CD28. Central memory T cells, which have previously encountered an antigen, express CD45RO, CD27 and CD62L and thus, retain their proliferative capacity. Effector memory T cells lack CD27 and CD62L which reduces their proliferative capacity.[25]

One unintended consequence of cytotoxic chemotherapy, is depletion of healthy T cells, including naïve and central memory T cell subsets, that have the most potent ability to respond to malignant antigens, have greater expansion potential and greater anti-cancer activity.[26-27] Numerous studies have shown superior persistence and anti-tumor activity with minimally differentiated T cells, including naïve, stem cell and central memory T cells.[28-30]
These observations also apply to CAR T cells, as study of determinant of outcomes revealed that frequencies of memory and naïve cells prior to CAR T manufacture appear to be associated with remissions.[31]

Heavily pre-treated patients with DLBCL exhibit a deficiency in naïve and minimally differentiated T cells, which renders their total T cell product collected by apheresis less able to expand during ex vivo culture as necessary during CAR-T cell manufacturing. T cells that are both CD27 negative and CD28 negative are considered senescent. Accordingly, culture of CD27negative/CD28negative cells

sorted from patients with DLBCL by FACS (fluorescent activated cell sorting) revealed no expansion, further validating these cells are senescent. Heavily pre-treated DLBCL patients have a significantly higher proportion of CD27/CD28 double negative T cells compared to healthy controls and newly diagnosed DLBCL patients.[16] DLBCL patients also have a much higher ratio of memory T cells to naïve T cells compared to healthy controls.[27] We reported decreases in CD27/CD28 co-expression upon T cells of one patient with DLBCL treated with CTL019 prior to subsequent CAR T decay.[32] In this patient, 60% of her total CD8 cells and 20% of CD4 cells exhibited loss of both CD27 and CD28 expression, a phenotypic change heralding T cell senescence and a decay of CAR T numbers. Collectively, this body of literature suggests that expression of co-stimulatory molecules such as CD27 and CD28 represent a phenotypic marker denoting T cells with an underlying phenotype that is more capable of inducing CAR T- mediated remissions. Thus, strategies to enhance frequencies of naïve and memory cells prior to ex vivo expansion, resulting in fewer terminally differentiated cells during expansion, can help improve the quality of T cells needed for manufacturing.[27]

3.1 Study Rationale

Relapsed/Refractory Diffuse Large B Cell Lymphoma (DLBCL) has a dismal prognosis, especially with relapse/refractory disease after autologous stem cell transplantation. Recently, a new adoptive cell transfer therapy, CAR-T cells, that manufactures a patient's T cells to express artificial receptors on their cell surface has shown promising results in patients that relapse or have refractory disease. However, there are subset of patients that fail to manufacture a sufficient amount of CAR-T cells ex vivo, have poor expansion in vivo or lose persistence of their CAR-T cells after infusion. This has been attributed to relapsed/refractory DLBCL patients having a predominance of more differentiated T cells that are senescent and have poor expansion potential for CAR-T cell manufacturing.
This pilot study will examine if a 2-week exposure to Duvelisib, will favorably change a patient's T cell phenotype for manufacturing of more potent CAR-T cells for relapsed/refractory DLBCL and relapsed/refractory follicularlymphoma patient receiving commercial tisagenlecleucel.

3.2 Clinical Experience

3.2.1 Pre-Clinical Studies

Based upon this rationale, a series of preclinical studies involving *ex vivo* culture of mononuclear cells from healthy volunteers and patients with DLBCL, we showed that the addition of duvelisib, an FDA-approved PI3K delta and gamma inhibitor, significantly augmented overall expansion of T-cells from healthy donors and DLBCL patients.[16] Phenotypic analysis of these cells revealed increased frequencies of non-senescent, naïve and memory T-cells that express both CD27 and CD28.[16] Duvelisib enhanced expansion of T cells from patients with DLBCL, while increasing expression of co-stimulatory molecules. More recently, we have shown that incubation with pharmacologically achievable and clinically relevant doses of duvelisib recapitulated the effect of duvelisib on T-cell expansion in healthy donors and patients with CLL (Funk et al., SITC 2019; unpublished data).
To assess the influence of PI3K delta and gamma inhibitor during *ex vivo* T cell culture, dose-response experiments of duvelisib or idelalisib (PI3K delta inhibitor) assessing the influence of these drugs upon T cell number and quality across logarithmic scales revealed a dose-dependent increase in the frequency of both CD8 positive T-cells and CD3 positive but CD4 negative CD8 negative cells, with corresponding decreases in CD4 cells (Funk et al., SITC 2019;unpublished data). These differences in the ratios of these T cells are particularly observed at doses of PI3K inhibitor sufficient to inhibit both PI3K delta and gamma. In a survey of the literature, Stock et al. (2019) reported a similar observations in that the ratio of CD8:CD4 T cells from patients with CLL increased when cultured with 1μM idelalisib, such that ratios of CD8:CD4 T cells became more similar to those observed T cells cultured from healthy volunteers.[33] Of note, 1μM idelalisib is sufficient to inhibit both

PI3K delta and gamma, but idelalisib cannot be administered at doses that achieve drug levels sufficient to inhibit PI3K gamma. Further analysis of the CD3 positive CD4 negative CD8 negative subset revealed that duvelisib (and idelalisib) significantly increase absolute numbers of Gamma Delta T-cells following 10 to 15-day *ex vivo* culture, particularly at doses sufficient to inhibit both PI3K delta and gamma (unpublished data). The T-cells expanded with a PI3K delta inhibitor (idelalisib) have improved survival following transfer to NSG mice as well as enhanced cytotoxicity against lymphoma targets using human and murine preclinical model systems.[16]

In summary, a body of preclinical literature and data suggest that modulation of the PI3K pathway, utilizing duvelisib, an isoform-selective inhibitor of PI3K delta and gamma, represents a strategy with potential to enhance the phenotype and expansion of T cells from patients with DLBCL and relapsed/refractory follicular lymphoma, which may enhance CAR T cell mediated outcomes. In an effort to translate these preclinical observations to the clinic, we hypothesize that 8 to 15 days of duvelisib exposure in patients with DLBCL or relapsed/refractory follicular lymphoma will enhance frequencies of T cells with replicative potential, so that mononuclear apheresis product collected for CAR-T manufacture following duvelisib exposure will result in faster manufacturing time than historical controls. We predict that one benefit of a reduced manufacture duration will be enhanced viability of the final CAR T cell product. Further, we hypothesize the enhanced yield of metabolically fit T cells will lead to generation of CAR T cells that will exhibit enhanced in vivo persistence and proliferation, significant since these factors are associated with longer remissions. Further, we predict infusion of CAR-T-cell product generated from patients pre-treated with duvelisib will not result in significantly different levels of CRS or neurotoxicity compared to patients treated with CAR-T-cells manufactured from a mononuclear cell apheresis product collected without prior exposure to PI3K inhibitors.

3.2.2 Pre-Clinical Pharmacology of Duvelisib and T Cell Expansion

Duvelisib is a highly potent dual PI3K delta and gamma inhibitor with a whole blood IC_{50} of 0.4μM for inhibition of the delta subunit and whole blood IC_{50} of 1.6μM for inhibition of the gamma subunit (Pachter & Weaver, SITC 2018). We have seen optimal T cell expansion at duvelisib concentrations of 40nM to 0.4 μM at 14 days.

3.2.3 PI3K Inhibitors in Clinical Settings

PI3 kinase (PI3K) inhibitors are FDA-approved for treatment of relapsed follicular lymphoma (FL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Orally bioavailable drugs are typically dosed once or twice a day with the goal of inhibiting signaling through the PI3K-AKT pathway causing reduction in the growth of malignant lymphoma cells and induction of apoptosis. PI3K inhibitors are generally well tolerated and can be given for weeks to months as continuous therapy without significant hematological toxicity. One common feature of treatment with PI3K inhibitors is the development of late autoimmune disease, including colitis, pneumonitis and rash, by blockade of differentiation into regulatory T cells which are necessary for self-tolerance and down-regulation.[34]

4. Study Intervention/Investigational Agent

4.1 Description

4.1.1 Duvelisib

Duvelisib is an oral PI3K inhibitor. FDA approved duvelisib (Copiktra, IPI-145) on September 24, 2018. Duvelisib is approved for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) after at least two prior systemic therapies, and relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies. Refer to the approved labeling for more details on specific indications and for detailed information on duvelisib.

4.1.2. Tisagenlecleucel Product

Tisagenlecleucel is an autologous cellular immunotherapy product that is comprised of CD3+ T cells that have undergone ex vivo T cell activation, gene modification, expansion md formulation in infusible cryomedia. The transgene to be expressed via lentiviral vector transduction is a CAR targeted against the CD19 antigen. The CAR contains a murine scFv that targets CD19 linked to a transmembrane region derived from the CD8 receptor, which is linked to an intracellular bipartite signaling chin of TCR-§ (or CD3-{) and 4-1BB intracellular signaling domains. The extracellular scFv with specificity for CD19 is derived from a mouse monoclonal antibody. T cells which we enriched from a patient leukapheresis unit are expanded ex *vivo* using commercially available magnetic beads that are coated with anti-CD3 and anti-CD28 monoclonal antibodies. The cells are transduced with the CD19 CAR lentiviral vector which ensures that only peripheral white blood cells enriched for lymphocytes are exposed to the vector. The residual non-integrated vector is washed away during the process. CTL019 cells will be expanded ex vivo for rip to 10 days. At the end of the culture, the CTL019 cells are depleted of magnetic beads, washed, concentrated, and cryopreserved. Results from a release testing procedure are required prior to release of the product for infusion.

4.1.3. Tisagenlecleucel Dose:

A dose of Tisagenlecleucel transduced cells for patients will consist of a single infusion of 1 to 5 $x10^8$ Tisangenlecleucel transduced cells.

4.1.4 Tisagenlecleucel Infusion:

The Tisagenlecleucel cell product will be prepared and released by the manufacturing facility to the study site approximately 3 to 4 weeks after manufacturing has commenced, provided all required safety and quality release criteria have been met. Upon receipt of the cryopreserved CTL019 cell product, an inventory must be performed, and a drug receipt log filled out and signed by the person accepting the shipment. The cryopreserved tisagenlecleucel should be kept in the vapor phase of liquid nitrogen until infusion.

Prior to CTL019 infusion the following criteria must be met:

1. All patients must undergo a rapid influenza diagnostic test within 10 days prior to the pined CLT0l9 infusion. If the patient is positive for influenza, oseltamivir phosphate or zanamivir should administered for 10 days as preventative treatment. The patient must complete their 10 -day preventative treatment course **prior** to receiving tisagenlecleucel. The test does not need to be repeated prior to infusion however, if flu-like or respiratory signs and symptoms are present, CTL019 infusion should be delayed until the patient is asymptomatic.
2. COVID-19 screening will occur prior to duvelisib initiation [see section 5.6]. Based on medical assessment, CTL019 infusion will be delayed in symptomatic patients (symptoms including but not limited to fever, cough, sore throat, loss of taste/smell, headaches, myalgias) suspected to have active COVID-19 disease until the patient is asymptomatic.
3. Patient should not experience a significant change in clinical status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of adverse events associated with experimental cell infusion.

4. Rapidly progressing patients, or patients experiencing laboratory abnormalities after enrollment, that in the opinion of the treating investigator or PI may impact patient safety or the patients' ability to receive the infusion, may have their infusion delayed until both the treating investigator and PI determine it is clinically appropriate to proceed with the infusion.
5. Patients experiencing toxicities from their preceding lymphodepleting chemotherapy will have their infusion schedule delayed until these toxicities have resolved. The specific toxicities wanting delay of infusion include:
   a. Pulmonary: Requirement for supplements oxygen to keep saturation greater than 91% or presence of progressive radiographic abnormalities on chest x-ray
   b. Cardiac: New cardiac arrhythmia not controlled with medical management
   c. Hypotension requiring vasopressor support
   d. Uncontrolled active infection, as evidenced by positive blood cultures for bacteria, fungus, or PCR positivity for viral DNA in blood within 72 hours of infusion, or clinical or radiographic evidence of active infection.

   Following lymphodepleting chemotherapy patients must not have progressive disease in order to receive infusion, as this will potentially put them at an unacceptable risk for severe CRS. Patients should not receive infusion if they exhibit significant progression of disease following lymphodepleting chemotherapy as evidenced by:

   a. Significant increase in nodal disease
   b. Significant increase in extra-nodal disease
   c. Occurrence of new lymphoma manifestations
   d. Clinical evidence of CNS disease
6. If patients are taking any of the following medications, their infusion must be delayed until the medications have been stopped according to the below:
   a. Steroids: Therapeutic doses of steroids must be stopped >72 hours prior to tisagenlecleucel infusion. However, the following physiological replacement doses of steroids we allowed: 6-12 mg/m^2/day hydrocortisone or equivalent
   b. Antiproliferative Therapy:
   c. All anti-proliferative therapies must have been stopped > 2 weeks prior to tisagenlecleucel infusion
   d. Immunosuppressive therapies: Any drug used for immunosuppression must be stopped > 4 weeks prior to tisagenlecleucel infusion (e.g. calcineurin inhibitors, methotrexate or other chemotherapy drugs, mycophenolate, steroids [see above], rapamycin, thalidomide or immunosuppressive antibodies such as rituximab, anti-TNF, anti-IL6 or anti-IL6R)
   e. CNS disease prophylaxis must be stopped 1 week prior to tisagenlecleucel infusion (e.g. intrathecal methotrexate).

Patients experiencing toxicities from their preceding chemotherapy will have their tisagenlecleucel infusion delayed until the above toxicities have been resolved. If any of the above criteria are not met and a period of delay is 4 or more weeks from completing lymphodepleting chemotherapy and the WBC is >1000/microL, the patient will need to be re-treated with lymphodepleting chemotherapy, and these criteria will need to be re-established prior to tisagenlecleucel infusion.

4.2 Drug/Device Handling

4.2.1 Acquisition and Accountability

Duvelisib will be provided by Secura Bio and will be packaged and labeled by Secura Bio.

The sponsor will acknowledge receiving the medication by completing and documenting forms indicating shipment content and condition. Records of duvelisib received at, dispensed from and returned by the study site will be documented in the drug inventory log (DIL). Duvelisib will be dispensed by clinical research staff per the protocol of the Winship Cancer Institute and dispensation of the study drug must be documented. Duvelisib should be taken at approximately the same times on each day and should be taken with 8 oz of water. Patients will be required to maintain a medication diary of each dose of medication. The medication diary (Appendix E) will be returned to clinic staff at the end of completion treatment or at the time of withdrawal from the study.

If a dose of duvelisib is missed by fewer than 6 hours, the missed dose can be taken right away and the next dose taken on schedule. If a dose is missed by more than 6 hours, the dose is skipped the next dose taken at the usual time. Patients will not be allowed to make up missed doses and a missed dose should also be recorded in the patient's diary. Incorrect dosing should also be reported in the patient's diary and documented in the case report form. Damaged medication will be replaced.

Patients will be asked to return all unused duvelisib and packaging at the end of the study or at the time of study treatment discontinuation. Duvelisib supply will be disposed of per Winship's Investigational Drug Service (IDS) SOP. Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver (collection of drug diary) will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit. Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

4.2.2. Formulation, Appearance, Packaging and Labeling

Duvelisib comes in two strengths: 15mg and 25mg. Patients will be provided twenty-eight (28) 25mg tablets. The contents of the label will be in accordance with regulatory requirements.

4.2.3 Product Storage and Stability

Duvelisib will be stored at the Emory Investigational Pharmacy. Duvelisib will be stored at room temperature between 20-25 degrees Celsius.

4.2.4. Safety of Duvelisib

Immune related toxicities are the most common non-hematological adverse event (AE) with duvelisib. Infection, elevated AST/ALT and diarrhea are the most common non-hematological AEs. The rates of diarrhea ranged from 42-51% in clinical trials with a median onset of 2.2-4 months.[35,36] The median time of onset for AST/ALT elevation was 1.2 months and occurred in 39% of patients in one phase I clinical trial.[35] Other non-hematological AE's that have been reported include maculopapular rash, pyrexia and colitis. Neutropenia was the most common hematological AE, occurring in 29%-39% of patients in clinical trials. Infections has also been reported in 61-69% of patients with upper respiratory tract infections and pneumonia being the most common infections.[36,37] There have also been reports of Pneumocystis jirovecci with the use of duvelisib.

5. Procedures Involved

5.1 Study Design

This is an open-label pilot clinical trial prospective study of treating patients with relapsed/refractory DLBCL or relapsed/refractory follicular lymphoma with duvelisib at a dose of 25 mg p.o. b.i.d. for 8 to 15 days prior to collection of mononuclear cells by apheresis for the purpose of CAR-T manufacturing. The intended duration of duvelisib exposure is 2 weeks. The duration of duvelsib may be adjusted to a period between 8 and 15 days depending upon the schedule of apheresis, with the last dose of duvelisib on the day of apheresis.

5.2 Dosing and Administration

In the phase I study with duvelisib in hematological malignancies, the maximum tolerated dose (MTD) was 75mg BID. However, peak inhibition of the p-AKT pathway was not dose dependent and was maximally inhibited at 25mg BID, and this is the FDA approved dose.[35]

5.3 Interruption/Disruption of Treatment

Duvelisib is a BID medication. Doses that are missed or not absorbed (i.e., vomiting) will not be made up with additional dosing after the 8 to 15 day study period.

Duvelisib can be stopped for any clinically significant toxicity, including if any of the following are observed:

- Grade 3 or 4 hematologic toxicity (19) as defined by the CTCAE version 5.0)
- Grade 3 or 4 non-hematological toxicity

For grades 1-2 as defined by the CTCAE, will not have any dose modifications and will be treated with supportive care. If study drug is stopped due to an AE, it will not be resumed, and the patient may proceed to leukapheresis on schedule. No allowance will be made for dose interruptions

5.4 Dose Modification

No dose modifications will be allowed on this study.

5.5 Concomitant medication

5.5.1 Acceptable Concomitant Medications

Duvelisib is a moderate inhibitor of CYP3A4 and monitoring of patients on sensitive medications that are CYP3A4 substrates will be required. Please Appendix B for known substrates of CYP3A. Concomitant medication (including prescribed, over the counter, herbal or vitamin supplements) used by the patient prior to 14 days to enrollment are permitted. All medications should be reported to the investigators and recorded in the concomitant medications page.

5.5.2 Prohibited Medications and Food

Patients on strong inducers or inhibitors of CYP3A within 14 days of starting duvelisib are excluded from the study. Concomitant use of medications known to be strong inducers or

inhibitors of CYP3A should be avoided unless deemed to be necessary by the PI. In this instance, patients should be carefully monitored for reduced drug efficacy or SAE from drug-drug interaction. Please see Appendix B for known potent inhibitors and inducers of CYP3A. Other anti-neoplastic drugs, radiotherapy and other investigational drugs are prohibited during the study period.

5.5.3 Supportive Medications

Because of increased incidences of PJP pneumonia, patients on study will be provided with PJP prophylaxis while on treatment with duvelisib. Following completion of duvelisib, PJP prophylaxis will be stopped if CD4+ T cell count is greater than 200 cells/microL.

5.6 Study Procedures

Screening Phase:

All screening evaluations must be conducted and reviewed by the primary investigator to confirm that patients meet the eligibility criteria. The following procedures will be performed during the screening visit:

- Informed Consent
- Medical History, Physical Exam, Assessment of Performance Status
- Electrocardiogram (EKG)
- Labs: Complete Blood Count (includes hemoglobin, platelets, and white blood cell count with differential), Comprehensive metabolic panel (includes sodium, potassium, chloride, creatinine, AST, ALT total bilirubin and alkaline phosphatase), Coagulation Testing (PT/INR, PTT), Thyroid Stimulating Hormone (TSH)
- T cell count phenotyping via flow cytometry
- Pregnancy Test (for women of childbearing potential)
- Infectious Work Up: HIV antigen/antibody, Hepatitis C antibody and Hepatitis B antibodies with viral loads (if known history of treated Hepatitis B or C).
- COVID-19 screening by PCR: During the screening period within 7 days of initiation of duvelisib.
    - If asymptomatic and PCR negative: Ok to proceed
    - If PCR+ and:
        - *Asymptomatic*: Wait 14 days and initiate duvelisib
        - *Symptomatic:* Wait 14 days *after resolution of symptoms* and initiate duvelisib
        - A negative PCR is not required after a 14 day wait period

Please see section 1.2 (Table 1) for schedule for screening and pre-screening assessments. Pre-screening assessments will be completed within two weeks of initiation of duvelisib treatment.

Treatment Phase:

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments (Section 1.3, Table 1).

- Brief medical history
- Symptom-directed physical exam

- ECOG Performance Status
- Vitals signs, weight
- Review of prior/concomitant medications
- Labs: Complete Blood Count (includes hemoglobin, platelets, and white blood cell count with differential), Comprehensive metabolic panel (includes sodium, potassium, chloride, creatinine, AST, ALT total bilirubin and alkaline phosphatase), Thyroid Stimulating Hormone (TSH)
- T cell count and phenotyping (days 1 and 15 only)
- AE monitoring (days 8 and 15)

Post CAR-T 19 Cell Infusion Assessments

Procedures to be conducted during the post CAR-T 10 cell infusion phase of the study are presented in the Schedule of Assessments (Section 1.3 Table 2).

- CAR T 19 PCR
- CAR T phenotyping
- PET/CT or CT (day 90 only post CAR T)

5.7 Description of Study Procedures

Definition of Study Assessments

All patients will be closely monitored for safety and tolerability throughout the study. Patients will continue dosing until they experience intolerable AE's, patient withdrawal or termination of the study. Patients may be discontinued from study treatment in the following situations: 1) patients has decided to withdrawal from the study, 2) Intolerable adverse events, 3) confirmed disease progression or lack of benefit, 4) pregnancy, or 5) severe noncompliance (including but not limited to receiving less than 75% of duvelisib doses (23/28 doses). The schedule of activities is listed in section 1.3.

Medical History

Medical history and demographics will be collected at screening. Medical history will include other significant co-morbidities, previous surgeries, cancer history, previous chemotherapy and outcomes, use of tobacco, alcohol and recreational drugs and any known toxin exposure. Demographics data will include age, sex and self-identified race/ethnicity.

Performance Status

The ECOG performance status (see appendix A) will be assessed at screening and throughout the study (days 1, 8 and 15 during treatment with duvelisib; days 7,14,28,42 and 90 post CAR-T infusion).

Physical Exam

Physical exam will include examination of all body systems, including assessment of general appearance, weight, height, head, neck, lymph nodes, heart, lungs, abdomen, extremities, skin and nervous system. A physical exam will be performed on screening and on days 1,8 and 15.

Laboratory Data

Blood samples for chemistry, hematology, viral serologies, leukocyte immunophenotyping and pregnancy (for pre-menopausal patients) will be analyzed at Winship Cancer Institute laboratory. The chemistry panel will include sodium, potassium, chloride, bicarbonate, glucose, BUN, AST, ALT, total bilirubin, total protein, thyroid stimulating hormone and magnesium will be tested at screening and on days, 1,8 and 15. Hematology panel includes complete blood count, including white blood cell count with differential (neutrophils, lymphocytes, eosinophils, basophils), red blood cell count, hemoglobin, hematocrit and platelet count will be tested at screening and days 1, 8 and 15.
Viral serologies will be tested at screening and include:

- HIV antigen/antibody
- Hepatitis B Panel (HBsAg, HBsAb, HBcAb and HBV DNA PCR if HBcAb is positive)
- Hepatitis C Panel (HCV Ab and HCV PCR if HCV Ab is positive)

Leukocyte immunophenotyping (via flow cytometry/fluorescence-activated cell sorting) will be done at screening and prior to apheresis for manufacturing CAR-T cells. This will determine the amount of B/T/NK cells and more specifically, the phenotypes and frequencies pre and post Duvelisib exposure.

Electrocardiogram

All ECG's will use a 12-lead tracing and performed during screening only. ECG will measure PR interval, QRS interval, RR interval and QTc. Additional ECG's and other cardiac tests can be performed as clinically indicated.

6. Data and Specimen Banking

Blood samples will be obtained and used for medical research by the investigators of this study. *Data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, Investigators may provide de-identified data and/or specimens to other researchers. Any information that could identify patients will not be included. If data or specimens are labeled with study ID, we will not allow other investigators to link that ID to identifiable information.*

Samples and data collected under this protocol may be used to study lymphoma. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study patients who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

The results of some study tests and procedures will be used only for research purposes and will not be placed in patient's medical record. For this study, those items include: research blood collection.

7. Tisagenlecleucel Apheresis Phase

7.1 Apheresis Collection

Patients will need to undergo leukapheresis within two (2) days of completion of the 8 to 15 day treatment of duvelisib. Apheresis will be performed at the Emory Center for Transplantation and Cell Therapy. Peripheral blood mononuclear cells will be collected for CAR-T cell manufacturing according to the standard of care. A single 2-4-hour leukapheresis will be performed on the COBE Optia with the intention of harvesting 3 x 10^9 white blood cells. If patients are unable to collect the necessary amount required for manufacturing, they can undergo a second leukapheresis. If patients are not able to collect enough product after the second leukapheresis, they will be considered unevaluable and replaced. After apheresis, the quantity of CD27/CD28 double positive T cells, CD4/CD8 double negative gamma delta positive T cells and CD4/CD8 double negative gamma delta negative T cells will be measured via flow cytometry. CAR-T cell manufacturing will be provided by Novartis and are expected to be ready 4 weeks after collection. Failure of the incoming apheresis material or outgoing product to meet the commercial specifications will be discussed with Novartis on a case by case basis.

7.2 Chemotherapy post-apheresis

Chemotherapy will be allowed as a bridging therapy after apheresis at the provider's discretion while the CAR T cells are being manufactured. Chemotherapy immediately prior to infusion of CAR-T cells for conditioning regimen (lymphodepleting) will be standard of care at the provider's discretion.

7.3 Tisangenlecleucel Infusion

CAR-T infusion will be administered per the standard-of-care protocol at Winship Cancer Institute. Patients will remain hospitalized per the standard of care and adverse reactions (neurotoxicity, CRS) will be managed per the standard of care.

7.4 Post-Tisangenlecleucel Monitoring

Following, discharge from the hospital patients will be followed per routine practice for CAR-T patients in the clinic or in-patient hospital services. Data on performance status, vital signs, clinical exam and any history of adverse events will be captured by chart review of clinical notes on days 7,14, 28, 42 and 90 post CAR-T (section 1.2, Table 2). Blood samples will be drawn on days 7,14, 28, 42 and 90 post CAR-T draws hematology tests and the presence of CAR-T 19 cells with PCR and flow cytometry.

8. Measurement of Effect

8.1 RECIST Criteria v 1.1

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by RECIST criteria. For the purposes of this study, patients will be re-evaluated at 3 months post CAR-T 19 infusion in comparison to a baseline scan.

8.1.1 Definitions

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received one infusion of CAR T 19 therapy, and have had their disease re-evaluated will be considered evaluable for response at 3 months (+/- 2 weeks) post CAR-T. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of CAR T infusion will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one infusion of CAR T 19 infusion, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

8.1.2. Disease Parameters:

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

8.1.3. Methods for Evaluation of Measurable Disease:

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT:
This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET:
While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

8.2 Evaluation of Disease:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.3 Evaluation of Best Overall Response:

The best overall response is the best response recorded from the start of the treatment until repeat imaging at 90 days. The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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: Patients 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.

8.4. Assessment of Engraftment:

Molecular studies (CAR-T 19 PCR) and immune phenotyping will be collected per the study protocol procedure. All samples will be processed by the Winship Cancer Institute Laboratory.

9. Sharing of Results with Patients

In general, study staff will not provide any individual results to patients (ex. outcome trial results or results from patient's samples studies). If something of urgent medical importance to the participating patients are found, the PI (or co-Is) will inform the patient, although we expect that this will be a very rare occurrence. Samples and data will only be used for research.

10. Study Timelines

10.1 Duration of therapy

We anticipate each individual patient's duration of therapy to be approximately 5 months. In the absence of treatment delays due to adverse event(s), patients will be followed until any one of the following:

- Death
- Unacceptable toxicity
- Symptomatic deterioration
- Investigator's decision to discontinue treatment
- Patient decision to discontinue treatment
- Patient withdraws consent
- Lost to follow up

In the event of a patient's withdrawal, the Investigator will make every effort to complete the End of Treatment procedures specified in the Schedule of Events.

10.2 Duration of follow-up

Patients will be followed for approximately 90 days after infusion of tisagenlecleucel product.
Patient records may be reviewed until death to assess progression and survival. Survival information may be collected by clinic visit, email, or telephone after ending protocol treatment and until the study is terminated, the patient dies, or the patient is lost to follow-up.

A patient will be considered lost to follow-up if he/she fails to return for three scheduled visits and is unable to be contacted by the study site staff after three attempts at contact by phone.
The following actions must be taken if a patient fails to return to the clinic for a required study visit:
The site will attempt to contact the patient and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to and/or should continue in the study.

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.
- Immunogenicity samples will be taken as per schedule of events

Patients who have not initiated a new antineoplastic regimen will have the following assessments:
• Radiologic tumor assessments at 90 days
• In case of a clinically significant AE, patient will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drug(s). If the patient discontinues study drug for a clinically significant AE, the patient will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

11. Inclusion and Exclusion Criteria

11.1 Inclusion Criteria

- Patients must have a biopsy proven diagnosis of relapsed/refractory DLBCL or relapsed/refractory follicular lymphoma and be eligible to receive commercial tisagenlecleucel (Kymriah).
- 18 years of age or older
- ECOG <2
- Patients must have normal organ function as defined as:
  - Serum Cr <2.0 mg/dL
  - AST/ALT < 2x ULN
  - Total Bilirubin <2.0 mg/dL
- Patients with a hemoglobin >8 g/dL, platelet count >50K/mcl, an absolute neutrophil count (ANC) >1,000/mm^3 and an absolute lymphocyte count (ALC) >300/mm^3
- Completion of all previous therapy (including surgery, radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of their DLBCL or relapsed/refractory follicular lymphoma ≥ 2 weeks before the start of duvelisib. There is no limit on how many previous lines of treatment a patient may have received.

- The effects of duvelisib on the developing human fetus are unknown. For this reason, women of child-bearing potential (WOCBP) must have a negative serum or urine pregnancy test prior to starting therapy. WOCBP and men must agree to use highly effective contraception (hormonal or barrier method of birth control or abstinence) from enrollment into this study until at least 12 months after tisagenlecleucel infusion and until CAR-T cells are no longer present by qPCR on two consecutive tests (qPCR tests will be available upon request).
  - A woman of childbearing potential (WOCBP) is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months.
  - WOCBP must have a negative pregnancy test within 24 hours of leukapheresis, lymphodepletion (if performed) and tisagenlecleucel infusion (if lymphodepletion not performed).
  - Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
  - All men treated or enrolled on this protocol must agree to use highly effective contraception from enrollment into this study until at least 12 months after tisagenlecleucel infusion and until CAR-T cells are no longer present by qPCR on two consecutive tests (qPCR tests will be available upon request).

<u>The patient must be willing to comply with the fertility requirements and contraceptive options below:</u>
- Female patients identified as WOCBP must be willing to use two adequate barrier methods of contraception to prevent pregnancy or agree to abstain from heterosexual activity (total abstinence).

- Total abstinence is permitted when this is in line with the usual practice and lifestyle of the patient. Periodic abstinence (i.e, calendar, ovulation, post-ovulation methods) and withdrawals are not acceptable forms of contraception.
- Sterilization:
    - Female sterilization includes having had surgical bilateral oophorectomy and/or bilateral salpingectomy with or without a hysterectomy, a total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, patients are eligible only when the reproductive status of the woman has been confirmed by a follow-up hormone assessment.
    - Male sterilization with vasectomy must occur at least 6 months prior to screening. For female patients on the study, the vasectomized male partner should be the sole partner.
- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception, or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of contraception that comparable efficacy (failure rate <1%). In case of oral contraception, the woman should be stable on the same pill for a minimum of 3 months prior to enrollment on the study.
- Sexually active males must use a condom during intercourse from enrollment into this study until at least 12 months after tisagenlecleucel infusion and until CAR-T cells are no longer present by qPCR on two consecutive tests (qPCR tests will be available upon request). A condom is required of all sexually active male patients to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner.

The patient must be willing to comply with the following requirements:

- Patients must agree not to donate blood, sperm/ova or any other organs while taking protocol therapy and for at least 12 months after stopping treatment.
- Willingness and ability of the patient to comply with scheduled visits, drug administration plan, protocol specified laboratory tests, other study procedures and study restrictions.
- Evidence of personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed on the procedures to be followed, the experimental nature of the therapy, alternative, potential risks and discomforts, potential benefits and other pertinent aspects of study participation.

11.2 Exclusion criteria

- Primary Central Nervous System Lymphoma
- Patients with CNS Involvement of Lymphoma
- History of autoimmune disease, including but not limited to:
    - Inflammatory Bowel Diseases (Crohn's Disease, Ulcerative Colitis, Celiac Disease)
    - Systemic Lupus Erythematosus
    - Grave's Disease
    - Myasthenia Gravis
    - Rheumatoid Arthritis
    - Wegner's Syndrome
- Patients with history of drug reaction and eosinophilia systemic syndrome (DRESS) or toxic epidermal necrolysis (TEN)
- History of Human Immunodeficiency Virus (HIV), active Hepatitis C Infection or active Hepatitis B infection as defined by:
    - Patients with a positive hepatitis B surface antigen [HBsAg] or hepatitis C antibody [HCV Ab] will be excluded

  - Patients with a positive hepatitis B core antibody (HBcAb) must have negative hepatitis B virus (HBV) deoxyribonucleic acid (DNA) to be eligible and must be periodically monitored for HBV reactivation by institutional guidelines
- Patients with known active cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection (i.e., subjects with detectable viral load)
- Patients with ongoing treatment for systemic bacterial, fungal or viral infection
- Patients with history of immune or drug mediated colitis, hepatitis or pneumonitis
- Patients with history or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function
- Patients with previous treatment with a PI3K inhibitor
- Patients currently on immunosuppressive therapy, including steroids
- Previous CD 19 directed therapy
- Patients who have had chemotherapy or radiotherapy within 2 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier (*i.e.*, have residual toxicities > Grade 1).
- Patients receiving any other investigational drugs.
- Pregnant women are excluded from this study because duvelisib is 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 duvelisib, breastfeeding should be discontinued if the mother is treated with duvelisib and breastfeeding should not be resumed until at least 1 month after last dose of duvelisib.
- Patients with history of chronic liver disease or veno-occlusive disease
- Patients that are unable to receive prophylactic treatment for pneumocystis, herpes simplex virus (HSV), or herpes zoster "(VZV) at screening
- Patients with history of tuberculosis treatment within the 2 years prior to randomization
- Patients with prior surgery or gastrointestinal dysfunction that may affect drug absorption (e.g., gastric bypass surgery, gastrectomy). Subjects with clinically significant medical condition of malabsorption, inflammatory bowel disease, chronic conditions which manifest with diarrhea, refractory nausea, vomiting or any other condition that will interfere significantly with drug absorption.
- Concurrent administration of medications or foods that are strong inhibitors or inducers of cytochrome P450 3A (CYP3A). No prior use within 2 weeks before the start of study intervention
- Administration of a live or live attenuated vaccine within 6 weeks of randomization

12. Local Number of Participants

We will be recruiting 20 patients at Winship. We are expecting to have to enroll (consent) 30 patients to reach our recruitment goal of 20.. Patients will be registered after signing of the informed consent document and meeting all entry requirements.

13. Recruitment Methods

Investigators, nurses (CRNs), research coordinators (CRCs) and/or data managers review lists of patients who have DLBCL or relapsed/refractory follicular lymphoma and will determine if there are patients who might be eligible for the clinical trial. The CRN/CRC/data manager reviews accessible medical records to screen further for eligibility. The CRN/CRC reviews the eligibility with the physician.
Patients will be identified by their treating physicians. Clinical care team at Winship will inform potential patients about the known benefits and potential risks of a clinical trial as well as other available treatment options.

Some of the patients recruited for this protocol will be patients being treated at Emory and under the care of one or more of the study investigators. Some potential patients will be identified by their community treating physician and referred to Emory for possible participation in the clinical trial.

No incentives are provided to patients for trial participation.

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once a patient has been consented for a trial.
Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

14. Withdrawal of Patients

All study patients have the right to withdraw from the study at any time. The reasons for withdrawal must be documented in the case report form. Final study evaluations will be done at the time of withdrawal. The following are examples of early withdrawal from the study:

- Patient withdrawal of consent at any time
- Any medical condition that the primary investigator or sponsor believes may jeopardize the patient's health or safety if they continue in the study
- Non-compliance (frequent missed visit, doses)
- Pregnancy
- Rapid progression of disease (ie: increasing/symptomatic lymphadenopathy) that would require alternative treatment prior to CAR T cell leukapheresis
- Termination of the study by the primary investigator, sponsor or FDA

15. Risks to Participants

- **Additional blood draws** - The physical risk of drawing blood is local pain and bruising at the site of venipuncture. Qualified phlebotomists or designee will draw blood samples. Care will be taken to obtain these specimens in a safe and hygienic manner. A small number of people experience lightheadedness or fainting. There is a slight risk of infection. To minimize these risks, attempts will be made to draw study blood samples at the same time as blood draws needed for routine clinical care are obtained. Repeated blood drawing may be associated with iron deficiency anemia.
- **Data security-** Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating sites. Electronic files will be password protected behind an academic institutional firewall. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any

publications from this study will not use information that will identify subjects. Organizations that may inspect and/or copy research records maintained at the participating sites for quality assurance and data analysis include groups such as the National Cancer Institute (NCI) and Food and Drug Administration (FDA).

16. Potential Benefits to Participants

There is no guarantee of benefit to subjects who enroll in this protocol.

17. Data Management and Confidentiality

17.1 Source Documents:

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples include medical records (hospital records, office charts), laboratory results, imaging scans and reports, EKG's, patient diaries, videos, photographs, pharmacy dispensing, and other records, investigator or patient completed questionnaires involved in the clinical trial.

17.2 Case Report Forms:

The case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded and all entries will be recorded into an electronic data capture system by authorized personnel. The principal investigator is responsible for assuring that the data entered into the CRF are complete, accurate and that entries are updated in a timely fashion. Data will be entered in the clinical management system - Online Collaborative Research Environment (ONCORE)- per Winship SOP 4.2 Data Completion Metrics. OnCore will be used to record all study related information for all registered subjects, including their assigned patient ID and assigned dose cohort. All data submitted must be accompanied by supporting source documents, where applicable and as outlined in the protocol-specific monitoring plan. Data completion will be reviewed monthly. In situations where there are significant delays of data completion, the Associate Director of Clinical Research or the Director of Clinical Trials may temporarily suspend enrollment.
All data must be entered in the timeframe required at each site, but no later than 30 days following registration and each visit completion. All queries are to be resolved within 4 weeks of issue. The coordinating center multi-site coordinator will provide OnCore training and request access to the appropriate staff at the participating site.

17.3 Data Retention:

All study documents will be retained for at least two years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country.

17.4. Transmission of Data:

. Emory University will cover the cost of shipment of blood samples. All patient samples for T-cell phenotyping will be analyzed at Emory University to ensure uniform analysis. Clinical data (ORR and rates of CRS, neurotoxicity, ICU transfers) will be captured with chart review at both Emory University. Data will be uploaded onto OnCore.

17.5 Statistical Plan:

17.5.1 Study Design Endpoints

This is pilot study to examine if exposure to a dual PI3K delta and gamma inhibitor before CAR T cell leukapheresis leads to decreases in manufacturing time and enhanced expression of CD27/CD28+ T cells. Patients who receive at least 75% (23/28 doses) of duvelisib will be evaluable for final analysis. Patients who do not receive 75% of doses will be considered unevaluable and replaced. Patients who do not undergo leukapheresis within two (2) days of completion of the 8 to 15 days of duvelisib will be considered unevaluable and replaced. All patients with any exposure to duvelisib will for evaluable for toxicity (please see section 13.3 on grading of toxicities).

17.5.2 Analysis of Primary Endpoints

All patients that complete ≥75% of planned duvelisib doses and undergo leukapheresis within 2 weeks of duvelisib treatment completion will be included in the final analysis of the primary endpoint. The primary endpoint of the study to estimate the fold-change increase in CD27/CD28 double positive T cells following *in vivo* exposure to duvelisib from baseline to day 15. Our in vitro studies have shown that culturing DLBCL patients' T cells with 14 days of duvelisib increased the amount of CD27/CD28 double positive T cells from 12.2% to 32.7% (Petersen, et al, supplemental data). However, there are currently no *in vivo* background data to benchmark the expected fold-change CD27/CD28 double positive T cells over a 14-day window. Therefore, with 20 patients, this pilot study will be based on estimation on the fold change increase only and will not include a formal evaluation of the change against a null unpromising fold-change. However, we will consider this study promising if there is at least a two-fold increase in CD27+/CD28+ in at least 75% of patients.

17.5.3 Analysis of Secondary Endpoints

1). Descriptive statistics will be used to calculate the proportion of patients that completed at least 75% of duvelisib doses as documented by the patient pill diaries. The proportion along with an exact 95% confidence interval will be reported.

2). Descriptive statistics will be used to calculate the median manufacturing time from the 10 patients that completed at least 75% of duvelisib doses. The median will be reported along with the minimum and maximum manufacturing times.

3). A Wilcoxon signed-rank test will evaluate the change in proportion of CD27+/CD28+ and CD4-/CD8- T cells at baseline and at day 15

4). Descriptive statistics will be used to calculate the *in vivo* expansion and persistence of CAR-T 19 cells post infusion as measured by serial CAR-T 19 PCR measurements.

5). The ORR (complete response or partial response) will be summarized along with an exact 95% confidence interval. Disease response will be based on the RECIST criteria (version 1.1). Please see section 8.2 on the definitions of disease response.

6). The 90 day PFS and OS will be estimated using the Kaplan-Meier method and calculated with corresponding 95% confidence intervals. Please see section 8.3 on the definitions of progressive disease.

7). Descriptive statistics will be used to calculate the frequency of ICU transfers due to CRS and/or neurotoxicity. Descriptive statistics will also be used to calculate the frequency of administration of tocilizumab and/or corticosteroids use for CRS and/or neurotoxicity.

8). Descriptive statistics will be used to assess the frequency of all grade toxicities as defined by CTCAE (version 5.0).

17.5.4 Demographics and Baseline Characteristics

Summary statistics and frequencies for the following characteristics will be collected:

- ECOG
- Race
- Age
- Sex
- Past Medical History
- Current Medication List
- Number type, dose and dates of prior treatments
- Prior autologous stem cell transplant (ASCT)
- Molecular Subgroup (Activated B cell vs Germinal Center)
- BCL-2 alterations/overexpression
- BCL-6 alterations/overexpression
- C-MYC alterations/overexpression
- Double/Triple Hit Status
- Disease Stage
- History of lymphoma bone marrow involvement

17.5.5 Safety Analysis

Adverse event data will be described and graded per the NCI CTCAE 5.0 guidelines. For each adverse event, information to be collected includes event description, time of onset, clinician assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), current correlate laboratory values (regardless of hematologic or non-hematologic etiology), treatment of AE and time of resolution/stabilization of the event. Regardless of relationship, all AEs will be recorded with start dates occurring any time after patient receives any duvelisib. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. Adverse events will be summarized and described within each cohort. They will initially be reviewed regardless of attribution, but also whether they are possibly, probably, or definitely related to treatment. In addition, we will review all adverse event data that are graded as 3, 4, or 5 and classified as either “unrelated” or “unlikely to be related” to study treatment in the event of an actual relationship developing. The incidence of severe adverse events or toxicities will be described. We will assess the proportion of patients who experience grade 3 or higher non-hematologic toxicity. To assess tolerability, we will also capture the proportion of patients who go off treatment due to adverse events.

17.6 Data/Specimens:

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator. The study participant’s contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Data and/or data forms will be submitted in the clinical management system - Online Collaborative Research Environment (ONCORE)- per Winship SOP 4.2 Data Completion Metrics. All information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored. This will not include the participant’s contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Samples and data collected under this protocol may be used to study DLBCL and relapsed/refractory follicular lymphoma. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

18 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 Definition of Adverse Events (AE):

The ICH defines an adverse event as any unfavorable and unintended sign, including laboratory findings, symptoms or diseases temporally associated with the use of an investigational product. Adverse event severity will be graded per the using the CTCAE version 5 for toxicity and adverse event reporting.

Any adverse events, either observed by the investigator or reported by the patient, should be documented, including the intensity and duration of the AE, what steps were taken in regard to duvelisib and the outcome.

The principal investigator must review any laboratory abnormality for clinical significance. If the abnormality is deemed to be clinically significant, then the adverse event will be reported along with the actions taken in regard to study treatment and the outcome of the event. All AE's will began recording at the beginning of enrollment until withdrawal and/or completion of the clinical trial.

18.2 Definition of Serious Adverse Events (SAE):

A serious adverse event (SAE) is any adverse event, occurring at any time or dose that:

- Results in death
- Is life-threatening
- Requires prolonged inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent of significant disability/incapacity
- Is a congenital anomaly/birth defect or
- Considered to be a serious medical event by the investigator (may jeopardize the patient or require intervention to prevent one of the outcomes listed in the above definitions)

Any event that does not meet the above criteria should be consider a non-SAE. For any event that meets the above criteria, an SAE report should be completed detailing the start and stop dates of the SAE, relationship to the study drug, the measures taken and outcome.

18.3 Classification of an Adverse Event

Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Efforts will be made to associate all AEs with a particular study intervention. AE collection for duvelisib will occur from the time of enrollment until 15 days post duvelisib treatment and followed until resolution or stabilization. AE collection for tisagenlecleucel will occur from the time of CAR-T infusion until 90 post CAR-T cell infusion.

18.4 Adverse Event and Serious Adverse Event Reporting

Expectedness

The principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Adverse Event Reporting

From the time of enrollment until 90 post CAR-T cell infusion following cessation of study treatment all adverse events, that begin or worsen after informed consent, **must be recorded** by the investigator or designee at each examination on the Adverse Event case report forms (CRF)/worksheets. All serious

adverse events collected during this time frame will also be reported to both the study supporter Secura Bio (email to securabio@parexel.com) and cell manufacturer (Novartis)..

The investigator will make every attempt to follow all subjects with serious and non-serious adverse events for outcome. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form (or EOT/SEC/Survival Information in NOVDD). The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 13.2 and which seriousness criteria have been met (include for NCDS trials)

Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.

A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality

would still, by definition, be an adverse event and must be reported as such. Any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be **submitted on an SAE form** and assessed by PI in order to determine reporting criteria to regulatory authorities, IRB, DSMC, or Sponsor. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible. The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

All patients with serious adverse events must be followed up for outcome.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode **within 24 hours** of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form. Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

SAEs thought to be related to Duvelisib should be reported to Secura Bio at 844-9-SECURA

Due to possible increased potency and increased toxicity risk-profile of tisagenlecleucel manufactured from the mononuclear cell apheresis product collected following treatment with duvelisib, all SAE that are collected will be reported to Novartis within 24 hours according to the following Table:

Interventional Clinical Trial <u>WITH</u> Tisagenlecleucel	
Collection by Sponsor	**Transfer to Novartis**
• All SAEs • All non-serious AEs • All reports of drug exposure during pregnancy and pregnancy outcome. Pregnancy and pregnancy outcome should also be collected for the female partner of any male patient who was treated with tisagenlecleucel, provided consent has been obtained from the female partner. • All reports of abuse and misuse of an investigational medicinal product, other medication errors and uses outside of what is foreseen in the protocol (irrespective if a clinical event has occurred).	**Within 24 hours of awareness, transfer the following safety events:** • All collected SAEs in patients exposed to tisagenlecleucel • All collected reports of tisagenlecleucel exposure during pregnancy and pregnancy outcome. All collected reports of pregnancy and pregnancy outcome of the female partner of any male patient who was treated with tisagenlecleucel, provided consent has been obtained from the female partner. • All collected reports of abuse and misuse of tisagenlecleucel.

In particular, any episode of CRS or neurotoxicity grade 2 or greater observed within the first 100 days after tisagenlecleucel infusion will be reported to Novartis.

18.5 Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **<u>all</u>** the following criteria: Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information: Protocol identifying information: protocol title and number, PI's name, and the IRB project number; A detailed description of the event, incident, experience, or outcome; An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP. This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

18.6 The Data and Safety Monitoring Committee (DSMC)

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol as determined by CTRC, the DSMC review may occur every 6 months or annually. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP). The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data. The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

18.7 Multisite Monitoring Plan

At the time of study initiation at a non-Emory site, the Emory Sponsor, Winship regulatory specialist, and Winship research coordinators will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance. The participating site will have internal monitoring meetings. These meetings, which will include the participating site investigator, the clinical research coordinator and the regulatory affairs coordinator, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain a spreadsheet which will be de-identified and will summarize all the patient data for subjects actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual subject. The spreadsheet will be shared with the Emory PI via e-mail. Multi-Site Winship's MSC will perform an on-site or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (once annually onsite and three times remotely) until subject follow-up is terminated. Monthly reviews of data in OnCore will be conducted to ensure compliance or identify discrepancies.

At least monthly teleconferences between Emory PI and participating site Teleconferences will be conducted at least once monthly between the PI at Emory and the research team at the participating site(s). The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy. The PI at Emory will communicate with participating sites via monthly email. The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition, electronic copies will be sent via email to the principal investigators at each site.

19. Provisions to Protect the Privacy Interests of Participants

Patients will be assured of their voluntary participation in the study, their choice to answer or not answer any question, and the protocol for maintaining confidentiality.

Patient confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to patients. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

The study patient's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

20. Economic Burden to Participants

The study sponsor, supporter (Secura Bio), and cell manufacturer (Novartis) will not pay for certain items and services the subject may receive in this study. Patients will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for regular medical care. If subjects have insurance, Emory will submit claims to the insurance for items and services that the sponsor does not cover. Emory will send in only those claims for items and services that it reasonably believes the insurance will pay and that the sponsor, supporter, or cell manufacturer has not paid. The actual amount that participants have to pay depends on whether or not they have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if in a study. If a patient does not have insurance, Emory will review that particular case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if patients have to pay any costs for taking part in the study and what those costs will be.

21. Consent Process

The initial informed consent discussion will occur in Winship Cancer. At Winship Cancer Institute, the informed consent is an ongoing, interactive process rather than a one-time information session. The consent form document is designed to begin the informed consent process, which provides the patient with ongoing explanations that will help them make educational decisions about whether to begin or

continue participating in the trial. The research team knows that a written document alone may not ensure that the patient fully understands what participation means. Therefore, the research team will discuss with the patient the trial's purpose, procedures, risks and potential benefits, and their rights as a patient. The team will continue to update the patient on any new information that may affect their situation.

Consent will be obtained prior to any research-driven procedures. The investigator will assess the patient's capacity during his/her encounters with him or her. The investigator will give the person providing consent adequate opportunity to read the consent document before it is signed and dated.

It will be explained to prospective patients what the study involves research, the purpose of the research, the expected duration of participation, as well as the approximate number of patients to be enrolled. The study procedures, and identification of research procedures vs. non-research will also be thoroughly discussed. It will be explained to patients that participation is voluntary and that the patient may discontinue at any time.

Refusal to participate or withdraw will not involve a penalty or loss of benefits to which the patient is otherwise entitled. Refusal will in no way affect the patient's future care. The patient will also be told of the possible consequences of the decision to withdraw from the research, and procedures for orderly termination of participation.

Any significant new findings developed during the course of the research that may affect the patient's willingness to continue to participate will be provided. Also explained will be anticipated circumstances under which the patient's participation may be terminated by the investigator without the patient's consent.

Prospective patients will be provided with a description of any reasonably foreseeable risks or discomforts as well as a description of any benefits to the patient or to others that might be reasons expected from the research. Alternative procedures or courses of treatment will also be thoroughly discussed.

Prospective patients will also be given detailed information describing the extent to which confidentiality of records identifying the participant will be maintained and what records may be examined by the research staff, IRBs, sponsor, their representatives, and possibly the FDA or OHRP.

Also communicated to the patient will be an explanation that emergency medical care will be arranged for a study-related illness or injury, and an explanation of whether funds are set aside to pay for this care and/or compensation, and if so by whom (e.g., sponsor, supporter, subject, or insurer). The participant is told the source of the study's funding.

All participants will be told of any additional costs that may result from participation in the research.

Non-English-Speaking Patients

A certified translator/interpreter will be present during the consenting process and all questions and concerns will be answered by the treating physician.

A short form in that specific language will be used. A certified translator/interpreter will be present during the consenting process and this will be documented. We will use what's available on Emory IRB website. For the languages that are not available, we will have the short form translated to that language and submit the IRB for review and approval prior to use. Process to Document Consent in Writing: Winship SOP 2.1: "Obtaining Informed consent for Interventional clinical trial" will be followed.

22. Setting

This pilot trial will be conducted at Emory University. Potential patients will be identified in hematology clinics, multidisciplinary cancer clinic and multidisciplinary tumor board at Emory University.

23. Resources Available

Emory University was founded in 1836 and is a national center for teaching, research, and service. Emory University has been named as one of the nation's top 25 universities for more than a decade by the U.S. News and World Report. Emory University research partners include the Georgia Institute of Technology, the University of Georgia, Morehouse School of Medicine, the US Centers for Disease Control and Prevention, Children's Healthcare of Atlanta, and the Georgia Clinical and Translational Science Alliance (GACTSA). Emory University researchers received $734 million from external funding agencies in fiscal year 2018, including approximately $441 million in funding from federal agencies, $359 million of this from the National Institutes of Health (NIH).

Winship Cancer Institute (Winship) is Georgia's first and only National Cancer Institute (NCI)-designated Comprehensive Cancer Center (P30CA138292) and is dedicated to the integration of innovative clinical and basic science research with outstanding patient care for the prevention, treatment and control of cancer. First designated in 2009, Winship's NCI designation was renewed in 2012 and 2016, achieving an "outstanding" rating. Winship earned the prestigious Comprehensive Cancer Center designation from the NCI in 2016, after demonstrating that its outstanding programs are reducing the cancer burden on the state of Georgia through research conducted in its laboratories, its clinical trial program, and its population-based science. The institutional support for Winship was rated as 'exceptional' by the review panel.

The **Winship Clinic Building C** houses the primary offices and clinical space for cancer services including the medical oncology, hematology, and surgical oncology clinics, the radiation oncology program, and the Winship Ambulatory Infusion Center. In summer 2017, Emory Healthcare completed the expansion of **Emory University Hospital Tower** on Clifton Road. This nine-floor facility adds 144 inpatient beds to the hospital, of which more than 80% are dedicated to cancer care. The hospital expansion also accommodates cancer patient-specific intensive care units, an expanded BMT Unit with peri-transplant clinics to facilitate continuity of care, and a 24-hour cancer urgent care center, which serves as both a triage facility and short stay treatment center for patients with cancer-related medical concerns.

The **Winship Phase I Unit**, on the fourth floor of the Emory University Hospital Tower, is the largest unit in Georgia dedicated to the earliest and most critical phase of new cancer therapy evaluation. There is space for 15 private treatment bays, four clinic rooms, its own lab for doing patient blood work, a dedicated secure medication room, computer workspace for research and other support staff, and a "fast track" bay with three chairs for rapid use in patients who, for example, might need only a research lab test done.

24. References

1). National Cancer Institute. NHL-Diffuse Large B Cell Lymphoma. https://seer.cancer.gov/statfacts/html/dlbcl.html.

2). Galaznik A, Huelin R, Stokes M, et al. Systematic review of therapy used in relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma. *Future Sci OA*. 2018;4(7):FSO322. Published 2018 Jul 19. doi:10.4155/fsoa-2018-0049

3). National Comprehensive Cancer Network. B Cell Lymphomas. Version 2.2019. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.

4). Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study [published correction appears in Blood. 2018 Feb 1;131(5):587-588]. *Blood*. 2017;130(16):1800–1808. doi:10.1182/blood-2017-03-769620

5). Armitage, JO, Gascoyne RD, Lunning MA, Cavalli, F. Non-Hodgkin Lymphoma. Lancet. 2017 Jul 15;390(10091):298-310. doi: 10.1016/S0140-6736(16)32407-2.
6). Schuster SJ, Svoboda J, Chong EA, et al. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. *N Engl J Med*. 2017;377(26):2545–2554. doi:10.1056/NEJMoa1708566
7). Brudno, JN, Kochenderfer, JN. Chimeric antigen receptor T-cell therapies for lymphoma. Nat Rev Clin Oncol. 2018 Jan;15(1):31-46. doi: 10.1038/nrclinonc.2017.128. Epub 2017 Aug 31.
8). Levine BL, Miskin J, Wonnacott K, Keir C. Global Manufacturing of CAR T Cell Therapy. *Mol Ther Methods Clin Dev*. 2016;4:92–101. Published 2016 Dec 31. doi:10.1016/j.omtm.2016.12.006
9). Fraietta JA, Lacey SF, Orlando EJ, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. *Nat Med*. 2018;24(5):563–571. doi:10.1038/s41591-018-0010-1
10). Cantley, LC. The Phosphoinositide 3-Kinase Pathway. Science (80-). 2002;296(May):1655-1658. doi:10.1126/science.296.5573.1655.
11). Cantley, LC. Obesity, Diabetes, and Cancer: The PI3K Connection. Lecture presented at: 2013 Breakthrough Prize in Medicine Symposium. December 13, 2013
12). Okkenhaug K. Signaling by the phosphoinositide 3-kinase family in immune cells. *Annu Rev Immunol*. 2013;31:675–704. doi:10.1146/annurev-immunol-032712-095946
13). Vanhaesebroeck B., Guillermet-Guibert J., Graupera M., Bilanges B. (2010). The emerging mechanisms of isoform-specific PI3K signalling. Nat. Rev. Mol. Cell Biol.11, 329–341. 10.1038/nrm288
14). van der Windt GJ, O'Sullivan D, Everts B, et al. CD8 memory T cells have a bioenergetic advantage that underlies their rapid recall ability. *Proc Natl Acad Sci U S A*. 2013;110(35):14336–14341. doi:10.1073/pnas.1221740110
15). Vangapandu HV, Jain N, Gandhi V. Duvelisib: a phosphoinositide-3 kinase δ/γ inhibitor for chronic lymphocytic leukemia. *Expert Opin Investig Drugs*. 2017;26(5):625–632. doi:10.1080/13543784.2017.1312338
16). Petersen CT, Hassan M, Morris AB, et al. Improving T-cell expansion and function for adoptive T-cell therapy using ex vivo treatment with PI3Kδ inhibitors and VIP antagonists. *Blood Adv*. 2018;2(3):210–223. doi:10.1182/bloodadvances.2017011254
17). Finlay DK, Rosenzweig E, Sinclair LV, et al. PDK1 regulation of mTOR and hypoxia-inducible factor 1 integrate metabolism and migration of CD8+ T cells. *J Exp Med*. 2012;209(13):2441–2453. doi:10.1084/jem.20112607
18). Rolf J., Zarrouk M., Finlay D. K., Foretz M., Viollet B., Cantrell D. A. (2013). AMPKalpha1: a glucose sensor that controls CD8 T-cell memory.*Eur. J. Immunol.*43 889–896. 10.1002/eji.201243008
19). Hukelmann JL, Anderson KE, Sinclair LV, et al. The cytotoxic T cell proteome and its shaping by the kinase mTOR. *Nat Immunol*. 2015;17(1):104–112. doi:10.1038/ni.3314
20). Salmond, RJ. mTOR Regulation of Glycolytic Metabolism in T cells. Front Cell Dev Biol. 2018; 6: 122.
21). Zhao Y, Niu C, Cui J. Gamma-delta (γδ) T cells: friend or foe in cancer development? [published correction appears in J Transl Med. 2018 May 8;16(1):122]. *J Transl Med*. 2018;16(1):3. Published 2018 Jan 10. doi:10.1186/s12967-017-1378-2
22). Landmeier S, Altvater B, Pscherer S, et al. Activated human gammadelta T cells as stimulators of specific CD8+ T-cell responses to subdominant Epstein Barr virus epitopes: potential for immunotherapy of cancer. *J Immunother*. 2009;32(3):310–321. doi:10.1097/CJI.0b013e31819b7c30
23). Zou C, Zhao P, Xiao Z, Han X, Fu F, Fu L. γδ T cells in cancer immunotherapy. *Oncotarget*. 2017;8(5):8900–8909. doi:10.18632/oncotarget.13051
24). Capsomidis A, Benthall G, Van Acker HH, Fisher J, Kramer AM, Abeln Z, et al. Chimeric antigen receptor-engineered human gamma delta T cells: enhanced cytotoxicity with retention of cross presentation. Mol Ther (2018) 26:354–65.10.1016/j.ymthe.2017.12.001

25). Jensen MC, Riddell SRDesign and implementation of adoptive therapy with chimeric antigen receptor-modified T cells. 24329794 *Immunological reviews*, 2014 Jan. : 257(1)127-44
26). Mackall, CL, Fleisher TA, Brown MR, Magrath IT et al. Lymphocyte depletion during treatment with intensive chemotherapy for cancer. Blood. 1994 Oct 1;84(7):2221-8.
27). Klebanoff CA, Scott CD, Leonardi AJ, et al. Memory T cell-driven differentiation of naive cells impairs adoptive immunotherapy. *J Clin Invest*. 2015;126(1):318–334. doi:10.1172/JCI81217
28). Gattinoni L, Lugli E, Ji Y, et al. A human memory T cell subset with stem cell-like properties. *Nat Med*. 2011;17(10):1290–1297. Published 2011 Sep 18. doi:10.1038/nm.2446
29). Gattinoni L, et al. Wnt signaling arrests effector T cell differentiation and generates CD8+ memory stem cells. Nat. Med. 2009;15:808–813
30). Klebanoff CA, Gattinoni L, Torabi-Parizi P, et al. Central memory self/tumor-reactive CD8+ T cells confer superior antitumor immunity compared with effector memory T cells. *Proc Natl Acad Sci U S A*. 2005;102(27):9571–9576. doi:10.1073/pnas.0503726102
31). Fraietta JA, Lacey SF, Orlando EJ, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. *Nat Med*. 2018;24(5):563–571. doi:10.1038/s41591-018-0010-1
32). Funk CR, Petersen CT, Jagirdar N, et al. Oligoclonal T Cells Transiently Expand and Express Tim-3 and PD-1 Following Anti-CD19 CAR T Cell Therapy: A Case Report. *Int J Mol Sci*. 2018;19(12):4118. Published 2018 Dec 19. doi:10.3390/ijms19124118
33). Stock S, Schmidt P, Schmitt A, et al. Idelalisib for optimized CD19-specific chimeric antigen receptor T cells in chronic lymphocytic leukemia patients. Int J Cancer. 2019. doi:10.1002/ijc.32201.
34). Greenwell I.B., Ip A., Cohen J.B. PI3K Inhibitors: Understanding Toxicity Mechanisms and Management. Oncology (Williston Park) 2017;31:821–828
35). Flinn IW, O'Brien S, Kahl B, et al. Duvelisib, a novel oral dual inhibitor of PI3K-δ,γ, is clinically active in advanced hematologic malignancies. *Blood*. 2018;131(8):877–887. doi:10.1182/blood-2017-05-786566
36). Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood*. 2018;132(23):2446–2455. doi:10.1182/blood-2018-05-850461
37). Horwitz SM, Koch R, Porcu P, et al. Activity of the PI3K-δ,γ inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma. *Blood*. 2018;131(8):888–898. doi:10.1182/blood-2017-08-802470

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.

As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

APPENDIX B: POTENT INHIBITORS AND INDUCERS AND SENSITIVE

	Sensitive Substrates	Moderately Sensitive Substrates
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir[f], ebastine, everolimus, ibrutinib, lomitapide, lovastatin[g], midazolam, naloxegol, nisoldipine, saquinavir[f],	alprazolam, aprepitant, atorvastatin[c], colchicine, eliglustat[e], pimozide, rilpivirine, rivaroxaban, tadalafil

CLINICAL SUBSTRATES OF CYP3A

Effect on CYP3A	Drug Class	Medications
Moderate to Strong CYP3A Inhibitors	Antibiotics	chloramphenicol, ciprofloxacin, clarithromycin, erythromycin,telithromycin
	Antiemetic	aprepitant
	Antifungals	ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole
	Antiviral protease inhibitors	amprenavir, atazanavir, boceprevir, cobicistat, darunavir, elvitegravir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tenofovir, tipranavir
	Calcium-channel blockers	diltiazem, mibifradil, verapamil
	Foods/herbs	grapefruit, grapefruit juice, Seville oranges
	Serotonin antagonist	nefazodone
	Tyrosine kinase inhibitor	imatinib
	Vasopressin antagonist	conivaptan
Moderate to Strong CYP3A Inducers	Antibiotics	nafcillin, rifampin
	Anticonvulsants	carbamazepine, phenobarbital, phenytoin
	Antiviral reverse transcriptase inhibitors	efavirenz, etravirine
	Endothelin receptor antagonist	bosentan
	Foods/herbs	St. John’s wort
	Wakefulness-promoting agent	modafinil

	simvastatin[g], sirolimus, tacrolimus, tipranavir[f], triazolam, vardenafil	
	budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir[f], lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	

APPENDIX C Drug Diary

Study ID:

[*Drug*] Pill Diary

Patient Initials:___ Patient ID: _____ Cycle: _____

Instructions:
Planned Daily Dose: __**mg**
REMINDERS:
1.
2.

Day	Date	Time	# of Tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Record all medications taken during this cycle for example prescriptions and over the counter including vitamins.

Name of Medication	Why did you take the medication?	Date Medication Started	Date Medication Stopped

If you have any questions, please call: _____

APPENDIX D: Procedure protocol for analysis of T cells and Correlate Studies Sample Collection Process

Procedure Protocol for Analysis of T-Cells and PMBCs for Winship Protocol #CTL019CUSO3T (Duvelisib Exposure to Enhance Immune Profiles of T Cells in Patients with Diffuse Large B Cell Lymphoma (DEEP T CELLS)

PBMC Cryopreservation with CryoStor Media (on days per schema below):

1. Suspend cells to be cryopreserved using mechanical or enzymatic dissociation.
2. Centrifuge cells to obtain cell pellet.
3. Remove supernatant.

Note: Remove as much culture medium as possible to reduce dilution of the CryoStor medium.

4. Isolation – Add **cold (2–8 °C) CryoStor medium** to a cell concentration range of 0.5–10x10^6 cells/ml for standard cell culture protocols. A higher cell concentration is possible with testing.

Note: CryoStor media contain DMSO, no additives are necessary.

5. Pre-freeze – Incubate cell suspension at 2–8 °C for ~10 minutes.
6. Nucleation – Lower sample temperature to –80 °C.
   a. Use a controlled rate freezer (–1 °C /minute) or similar procedure for most mammalian cell systems.
   b. The freezer should be pre-cooled to 2–8 °C.
   c. Ice nucleation within the sample (seeding) should be initiated at approximately –5 °C using a liquid nitrogen burst program setting on the controlled rate freezer or mechanical agitation (flick or tap) of the cryovial/sample container after 15–20 minutes at –80 °C.

Alternative Nucleation Procedures – cells can be frozen using stepwise freezing procedures.
Stepwise freezing procedures include:

   a. 2 hours at –20 °C followed by 2 hours at –80 °C or
   b. 3–4 hours at –80 °C in an isopropanol freezing container. The isopropanol container should be pre-cooled to 2–8 °C
   Ice nucleation – mechanical agitation (flick or tap) of the cryovial/sample container after 15–20 minutes at –80 °C.

7. Storage – Store the samples at liquid nitrogen temperatures (below –130 °C).

Note: Sample storage at –80 °C is only recommended.

8. Thawing - Thaw samples quickly in a 37 °C water bath. Sample should be thawed with gentle swirling of the sample until all visible ice has melted. Thaw time for a 1 ml sample in a cryovial is ~3 minutes.

Note: DO NOT allow sample to warm above chilled temperatures (0–10 °C). Cryovials should be cool to the touch when removed from the water bath. Passive thaw is **not** recommended.

9. Dilute cell/CryoStor mixture immediately with appropriate culture medium. This can be performed in a single step. The dilution medium should be between 20–37 °C. A dilution ratio of 1:10 (sample: medium) or greater is recommended.
10. Plate cells appropriately.
11. Culture the cells or use immediately.

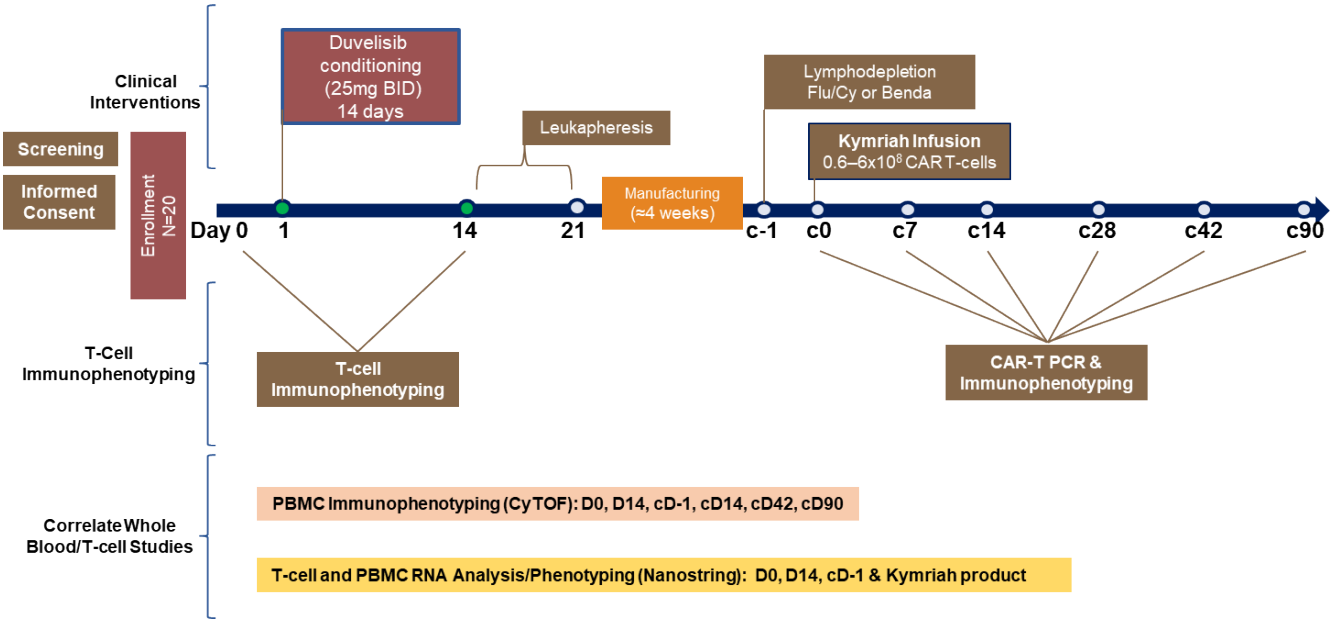
CAR-T PCR (on days per schema below)

Peripheral blood will be sent to Novartis for PCR analysis. Overnight shipment will occur directly from each clinical site to Novartis for analysis.

Collection for Correlate Whole Blood/T-cell Studies (on days per schema below)

Additional sample collection along with T-cell immunophenotyping samples per schema below for biomarker correlative studies and tissue banking:
- PBMC Immunophenotyping in 1x 10mL BD EDTA top tube (CyTOF)
- T-cell and PBMC RNA Analysis/Phenotyping in 2x 10cc (Nanostring)

All samples will be processed per manufacture protocols (CPT Tubes: Becton Dickinson, CyTOF MaxPar Direct Immune Profiling: Fluidigm, Nanostring Panels: Nanostring Technologies). Remaining serum, PBMCs, and T-cells will be centrally banked at Emory University.



APPENDIX E Abbreviations and definition of terms

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation or special term	Explanation
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System

Abbreviation or special term	Explanation
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction

Abbreviation or special term	Explanation
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCLC	Small cell lung cancer
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization