Masonic Cancer Center, University of Minnesota
Cancer Experimental Therapeutics Initiative (CETI)

FATE FT596 with Rituximab as Relapse Prevention in High Risk Patients after Autologous Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphoma

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Confidential

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Refer to the Procedures Manual for Participating Sites for a complete list of study personnel and contact information.

Revision History

Revision #	Version Date	Revision Details	Consent Revision
	Mar 13, 2020	Original to FDA	n/a
	Apr 08, 2020	In response to FDA IR April 6 2020	n/a
	Apr 09, 2020 am	In response to FDA IR April 8 2020 Additional edits: • Revise Section 8 – Tests and procedures to reflect more frequent follow-up and increased research related sample collection • Edits through-out to reflect a single dose of rituximab and a single dose of FT596	n/a
	Apr 09, 2020 pm	In response to the FDR IR April 9 2020 – original version to CPRC	
	May 20, 2020	CCPM and general edits before IRB submission: • Synopsis, Section 3, Section 8, Section12.1: make consistent throughout protocol that rituximab is given 2-3 days prior to FT596, clarify only on dose of FT596 is given in this study • Schema, Synopsis, Section 6.4, Section 10.4, Section 12.4: revise monitoring for excessive toxicity (stopping rules) is from day of transplant not day of FT596. • Schema, Section 3, Sections 6.2 and 6.3, Section 8 and other places: add a +/- 1 day window for Day 7 and Day 30 FT596 infusion to permit some flexibility of scheduling for individual patients • Section 6.1.2 – update FT596 administration language to be consistent without other Fate protocols • Section 7.2 Schema, Section 8.1 – add a Day 21 timepoint for disease reassessment, vascular access assessment, etc. for Component 1 to permit rituximab administration on Day 28 for Day 30 FT596. • Section 7.2 – add recommended IV hydration to reduce the risk of DMSO related toxicity • Section 7.3 – add monitoring of CRP and ferritin 3 times per week until resolution in the event CRS is diagnosed (with caveat missed testing will not be a deviation as patients maybe outpatient)- • Section 8.1 – remove KPS row, add row for concomitant medications, vascular access assessment, testing associated with CRS and neurotoxicity • Section 8.2 – refine research related samples and collection schedule • Section 10.7 – update expedited reporting table to reflect Advarra as IRB of record and other updates • Delete Appendix I as Karnofsky PS not assessed (not part of eligibility • Other minor edits and clarifications through-out (tracked)	Initial consent

Revision #	Version Date	Revision Details	Consent Revision
1	Oct 29 2020	• Synopsis, schema, Sections 3-5, Section 8 - General update to permit study consent/registration and enrollment after HCT • Section 7.3 – clarify IL-6 sample collection and update Table 1 tocilizumab administration guidelines for hypotension refractory to fluid boluses, add Actemra® (tocilizumab) prescribing info to References • Section 8.2 – add Day 28 CRP and ferritin, Add research samples at 3, 6, and 12 month post-transplant follow-up • Section 8,2 – delete the row for chimerisms from the research samples – update the 6 ml green top tubes with a new footnote 1 with instructions to use part of the green tops for PK samples (replacing chimerisms as testing done at the institutional level would not provide meaningful results). • Section 8.2 – move PRA anti-HLA antibodies testing from prior to transplant to prior to FT596, add baseline safety samples for Fate • Section 4.3 – correct wording “no requirement” for systemic immunosuppression during FT596 treatment period • Delete Section 5.3 and move wording to Section 5.2 • Minor edits to Section 8.1 removing unnecessary con med assessment time points and updating footnote 6 to match the schedule of vital sign monitoring to Section 6.1.2 • Section 10.7 – Delete row in required reporting table for DLT and SR reporting to the SAE coordinator as now automatically receives notification via OnCore. • Other minor edits and clarifications	Yes
2	Nov 30 2020	• Synopsis, Section 6.1, Section 9.2 and throughout protocol clarify rituximab may be Rituxan or any FDA approved biosimilars • Synopsis, Schema, Section 6, Section 8 – permit a +3 day window from the targeted FT596 targeted administration (Day 30 or Day 7 post-transplant) for the rituximab/FT596 “package”. Rituximab or an FDA approved biosimilar administration remains at 48-72 hours prior to the day of the planned FT596 infusion. • Other minor edits and clarifications	yes

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Key Abbreviations

Abbreviation	Definition
ABW	actual body weight
ADL	activities of daily living
AE	adverse event
Auto-HSCT	autologous hematopoietic stem cell transplant
CAR	chimeric antigen receptor
CFR	Code of Federal Regulations
CNS	central nervous system
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	diffusing capacity of the lungs for carbon monoxide
DLT	Dose limiting toxicity
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GvHD	graft-versus-host disease
HCT	hematopoietic cell transplantation
HSCT	hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IL-15RF	IL-15 receptor alpha fusion protein
IND	Investigational New Drug
IPI	International Prognostic Index
IRB	Institutional Review Board
IV	intravenous
LTFU	long-term follow-up
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NK	natural killer
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	progression free survival
PFT	pulmonary function test
RECIST	Response Evaluation Criteria in Solid Tumors
rhIL-15	Recombinant human interleukin-15
SAE	serious adverse event
SD	stable disease
SOC	standard of care
SR	stopping rule
TITE-CRM	time-to-event continual reassessment method
TRM	treatment related mortality
ULN	upper limit of normal

Protocol Synopsis

FATE FT596 with Rituximab as Relapse Prevention in High Risk Patients after Autologous Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphoma

Study Design:	This is a Phase I multi-center study to evaluate the safety of FT596 when given with rituximab as relapse prevention in patients who have undergone an autologous hematopoietic stem cell transplant (auto-HSCT) for diffuse large or high-grade B cell lymphoma. For the majority of participants, this study is presented to the patient and consent is signed at the time consent for the autologous transplant is obtained. Research related samples are collected prior to the start of conditioning on any consented patient. Alternatively, a patient may be consented and enrolled after the transplant provided the patient can begin treatment within their assigned window. The transplant procedures and follow-up are conducted per institutional standard of care. Participation in this study does not affect or impact the transplant, supportive care, and subsequent post-transplant care, except that, if post-transplant radiation therapy is planned, it must be delayed until after Day 100. FT596 is comprised of allogeneic natural killer (NK) cells expressing a CD19-targeted chimeric antigen receptor (CAR), a high-affinity non cleavable CD16 receptor (hnCD16), and an interleukin (IL)-15/IL-15 receptor alpha fusion protein (IL-15RF). FT596 is an off-the-shelf cellular product and expected to be uniform in composition. The mechanism of action is targeting B-cell tumor cells through direct cytotoxicity, CAR-mediated targeting of CD19 as well as through antibody-dependent cellular cytotoxicity (ADCC) in combination with rituximab for a dual-targeting approach. This study uses a single dose of the investigational product FT596 in the early post-transplant period. Rituximab or an FDA approved by biosimilar including Rituxan®, Truxima®, and Ruxience™ is given 2-3 days prior to FT596. The goal of this study is to 1) establish a maximum tolerated dose (MTD) of FT596 when given 30 days after transplant and 2) to confirm the MTD and safety of giving a single dose of FT596 at Day 7 post-transplant starting at one dose level below the MTD identified at Day 30. **Component 1: Identify the maximum tolerated dose (MTD) of FT596 when given as a single dose at Day 30.** Up to three FT596 dose levels are planned for Day 30 administration (with a +3 day window): (Dose Level 1: $9x10^7$ cells/dose, Dose Level 2: $3x10^8$ cells/dose, Dose Level 3: $9x10^8$ cells/dose with a Dose Level -1: $3x10^7$ cells/dose tested only if DLT at DL1).The maximum tolerated dose will be determined by using a modified continual reassessment method (CRM). Patients are enrolled in cohorts of 3 starting at Dose Level 1. A minimum of 28 days will separate each cohort. For Dose Level 1 a minimum of 28 days will separate each patient to assess for dose limiting toxicity (DLT). In subsequent cohorts, the 1st and 2nd patient will be separated by at least 28 days and at least 14 days will separate the 2nd and 3rd patient. Each new cohort of three patients will be sequentially assigned to the most appropriate dose based on the updated toxicity probabilities under the continuous reassessment method (CRM), and the MTD will be identified when the total sample size of 18 is exhausted or 6 patients are sequentially enrolled at the same dose. Dose limiting toxicity is defined as any of the following events within 28 days of FT596 dosing based on CTCAE v5: • Grade 4 hematologic toxicity lasting > 7 days (not including lymphopenia) • Grade 4 non-hematologic toxicity • Grade ≥3 FT596 Infusion Related Reaction • Grade 2 acute GVHD that requires steroid therapy >7 days or progression after 3 days of steroids or has partial response after 14 days of treatment • Grade ≥3 acute GVHD • Grade 4 cytokine release syndrome (CRS) • Grade 3 CRS that does not resolve to < Grade 2 in 72 hours

	• Grade 3 neurotoxicity • Grade 3 organ toxicity involving vital organs; cardiac, central nervous system and pulmonary which lasts longer than 7 days including Grade 3 Investigations (laboratory values) of any duration that indicate damage to vital organs. • Any Grade 3 non-hematological toxicity that does not resolve to ≤Grade 2 within 72 hours; excepting Grade 3 renal and hepatic toxicity which may take up to 7 days to resolve to ≤Grade 2 **Note:** Once enrollment is completed for Component 1, enrollment will be suspended. A summary for Component 1, including safety data (summary of DLT and SR events) will be provided to the FDA for review. Only after receiving their permission will Component 2 begin enrollment. If permission is not received, the study will end. **Component 2: To determine the safety of FT596 when given at Day 7 based on the MTD from Component 1.** Component 2 will use a similar design but identifies the MTD of FT596 when given as a single dose at Day 7 (with a +3 day window) post-transplant. Up to two dose levels of FT596 are planned (one dose level below the MTD from Component 1 and the MTD from Component 1). Any two sequential dose levels of FT596 may be included: Dose Level -1: $3x10^7$ cells/dose, Dose Level 1: $9x10^7$ cells/dose, Dose Level 2: $3x10^8$ cells/dose, Dose Level 3: $9x10^8$ cells/dose. The maximum tolerated dose will be determined by using a modified continual reassessment method (CRM). Patients are enrolled in cohorts of 3 starting at one dose level below the MTD of Component 1 (MTD-1). Only the MTD-1 and the MTD of Component 1 will be tested. A minimum of 28 days will separate each cohort. For the 1st cohort a minimum of 28 days will separate each patient to assess for dose limiting toxicity (DLT). In subsequent cohorts, the 1st and 2nd patient will be separated by at least 28 days and at least 14 days will separate the 2nd and 3rd patient. Each new cohort of three patients will be sequentially assigned to the most appropriate dose based on the updated toxicity probabilities. The MTD will be identified when the total sample size of 18 is exhausted or 6 patients are sequentially enrolled at the same dose. The DLT events for Component 2 are the same as in Component 1 except for the addition of: • Non-engraftment by Day 28 post-transplant **Monitoring guidelines for excessive toxicity (Stopping Rule events) Component 1 and Component 2 (ONLY POST FT596 EVENTS COUNT HERE))** The following events occurring after the FT596 infusion are measures of excessive toxicity based on Day 0 as the Transplant Day). Each component is monitored separately. • Mortality by Day 100 • Grade III-IV Acute GVHD by Day 100 • Any Grade 4 FT596 Infusion Related Reaction • Any Grade 4 Dose Limiting Toxicity (DLT) event • Grade 4 Lymphopenia (<200 cells/uL) at Day 100 • Engraftment failure by Day 28 (Component 2 only)
Study Products:	FT596 and rituximab (Rituxan or any FDA approved biosimilar)
Primary Objective:	The primary objective of this study is: Component 1: Establish a maximum tolerated dose (MTD) of FT596 when given 30 days after transplant. Component 2: Confirm the MTD and the safety of giving a single dose of FT596 at Day 7 post-transplant using one dose level below the MTD (MTD -1) or the MTD from Component 1.

Secondary Objectives:	• To evaluate the adverse events related to FT596 administered post auto-HSCT in combination with rituximab (Rituxan or an FDA approved biosimilar, e.g. Truxima and Ruxience). • To determine preliminary efficacy based on progression free survival (PFS) and relapse/progression at 12 months post auto-HSCT. • To determine the incidence of non-relapse mortality at 100 days and 1 year post auto-HSCT.
Correlative Objectives:	Correlative objectives include: • To evaluate persistence of FT596 in blood after each FT596 infusion by immunophenotyping and PCR up to 1 year. • To assess the association of FT596 cell persistence with safety and anti-tumor activity. • To assess the association of baseline clinical and tumor characteristics with safety and response endpoints following administration of FT596.
Key Inclusion Criteria: (at time of consent/ screening)	• Diagnosis of diffuse large B cell lymphoma or aggressive (high-grade) B-cell lymphoma for which an autologous stem cell transplant is planned or recently completed • High risk for relapse defined as at least one of the below: o Primary induction failure (no complete or partial remission at any point after diagnosis) o Initial remission duration < 12 months o Lack of complete metabolic (PET scan) response after 2-3 cycles of salvage chemotherapy o Evidence of *c-myc* and *bcl-2* and/or *bcl-6* re-arrangement (double hit or triple hit lymphoma) o Age-adjusted International prognosis index (IPI) 2-3 at relapse • Age 18 years or older at the time of signing consent. • Agrees to use adequate contraception (or evidence of sterility) at least 12 months after the last dose of rituximab. • Agrees and signs the separate consent for up to 15 years of follow-up (Long-term Follow-up study CPRC#2020LS052) • Provides voluntary written consent prior to the performance of any research related activities.
Key Exclusion Criteria: (at time of consent/ screening)	• Receipt of any investigational therapy within 28 days prior to the first dose of FT596 or planned use of an investigational therapy during the first 100 days after transplant • Planned post-transplant irradiation prior to Day +100 • Seropositive for HIV, active Hepatitis B or C infection with detectable viral load by PCR • Body weight <50kg • Known allergy to the following FT596 components: albumin (human) or DMSO • Unable to receive rituximab
Post-HCT Eligibility Confirmation	• No life-threatening medical issues (i.e. ongoing Grade 4 adverse events) where, in the opinion of the treating investigator, use of FT596 is not in the patient's best interest. • No active uncontrolled infection. • Adequate organ function post-transplant including: • alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤5 x ULN (Grade 2 CTCAE v5) • total bilirubin ≤1.5 x ULN (Grade 1 CTCAE v5) • serum creatinine ≤1.5 x ULN (Grade 1 CTCAE v5) • oxygen saturation ≥93% on room air • For Day 30 dosing only – CBC requirement consistent with engraftment (ANC>500, platelet>20,000 without transfusion support within previous 7 days). There are no CBC parameters for Day 7 dosing.
Enrollment Plan:	Component 1: a maximum of 18 patients, but most likely 12 if toxicity is as expected Component 2: a maximum of 18 patients, but most likely 12 if toxicity is as expected
Accrual:	It is expected 12-18 patients could be enrolled per year with two sites.

Study Schema

Treatment may be given as an inpatient or outpatient – there is no study driven requirement for a hospital admission.

Component 1 - FT596 at Day 30 Post Transplant to Identify MTD

***** Alternatively consent/initial screening may be done after HSCT – refer to Section 5.

Schedule for disease assessment around Day +21 to allow for rituximab to be given on Day 28

I FT596 at assigned dose* Note a +3 day window is permitted for FT596 dosing (i.e. Day +31, Day +32 or Day +33)

X Rituximab (Rituxan or an FDA approved biosimilar, e.g. Truxima and Ruxience) 375 mg/m^2 IV 2-3 days before FT596 (refer to Section 6.1 for details)

*Dose Levels for Identification of MTD

Dose Level	FT596 Cells per Dose	Enrollment Plan
-1	3 x 10^7 cells	Tested only if Dose Level 1 has DLT
1 (start)	9 x 10^7 cells	Enroll 3 patients at Dose Level 1 with at least 28 days between each of the 3 patients. Once the 28 day DLT assessment periods ends for all 3 patients, enroll the next cohort of 3 patients to the most appropriate dose based on the updated toxicity probabilities. A minimum of 28 days must separate the 1st and 2nd patients and a minimum of 14 days must separate the 2nd and 3rd patient within a cohort. The MTD is identified when the total sample size of 18 is exhausted or 6 patients are sequentially enrolled at the same dose.
2	3 x 10^8 cells	
3	9 x 10^8 cells	

Component 1 dose limiting toxicity is defined as any of the following events within 28 days after FT596 dosing based on CTCAE v5:

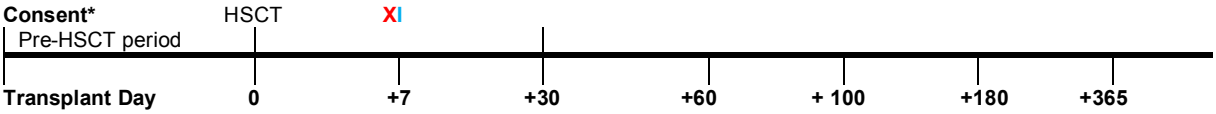
- Grade 4 hematologic toxicity lasting > 7 days (not including lymphopenia)
- Grade 4 non-hematologic toxicity
- Grade ≥3 FT596 Infusion Related Reaction
- Grade 2 acute GVHD that requires steroid therapy >7 days or progression after 3 days of steroids or has partial response after 14 days of treatment
- Grade ≥3 acute GVHD
- Grade 4 cytokine release syndrome (CRS)
- Grade 3 CRS that does not resolve to < Grade 2 in 72 hours
- Grade 3 neurotoxicity
- Grade 3 organ toxicity involving vital organs; cardiac, central nervous system and pulmonary that lasts longer than 7 days including Grade 3 Investigations (laboratory values) of any duration that indicate damage to vital organs.
- Any Grade 3 non-hematological toxicity that does not resolve to ≤Grade 2 within 72 hours; excepting Grade 3 renal and hepatic toxicity which may take up to 7 days to resolve to ≤Grade 2

Component 1 monitoring guidelines for excessive toxicity (Stopping Rule events) occurring after the FT596 infusion based on Day 0 as the Transplant Day (ONLY POST FT596 EVENTS COUNT HERE):

- Mortality by Day 100
- Grade III-IV Acute GVHD by Day 100
- Any Grade 4 FT596 Infusion Related Reaction
- Any Grade 4 Dose Limiting Toxicity (DLT) event
- Grade 4 Lymphopenia (<200 cells/uL) at Day 100

NOTE: Component 2 may not begin until after the FDA gives permission to proceed (refer to Section 6.3)

Component 2 - Safety of FT596 when given at Day 7 based on the MTD from Component 1



* Alternatively consent/initial screening may occur after HSCT – refer to Section 5

I FT596 at assigned dose* Note a +3 day window is permitted for FT596 dosing (i.e. Day +8, Day +9 or Day +10)

X Rituximab (Rituxan or an FDA approved biosimilar, e.g. Truxima and Ruxience) 375 mg/m^2 IV 2-3 days before FT596 (refer to Section 6.1 for details)

*Dose Levels for Identification of MTD at Day 7

Dose Level based on MTD from Component 1	Enrollment Plan
MTD – 1 Dose Level (Start)	Enroll 3 patients at Dose Level 1 with at least 28 days between each of the 3 patients. Once the 28 day DLT assessment periods ends for all 3 patients, enroll the next cohort of 3 patients to the most appropriate dose based on the updated toxicity probabilities. A minimum of 28 days must separate the 1st and 2nd patients and a minimum of 14 days must separate the 2nd and 3rd patient within a cohort. The MTD is identified when the total sample size of 18 is exhausted or 6 patients are sequentially enrolled at the same dose.
MTD	

Component 2 dose limiting toxicity is defined as any of the following events within 28 days after FT596 dosing based on CTCAE v5:

- Grade 4 hematologic toxicity lasting > 7 days (not including lymphopenia)
- Grade 4 non-hematologic toxicity
- Grade ≥3 FT596 Infusion Related Reaction
- Grade 2 acute GVHD that requires steroid therapy >7 days or progression after 3 days of steroids or has partial response after 14 days of treatment
- Grade ≥3 acute GVHD
- Grade 4 cytokine release syndrome (CRS)
- Grade 3 CRS that does not resolve to < Grade 2 in 72 hours
- Grade 3 neurotoxicity
- Grade 3 organ toxicity involving vital organs; cardiac, central nervous system and pulmonary that lasts longer than 7 days including Grade 3 Investigations (laboratory values) of any duration that indicate damage to vital organs.
- Any Grade 3 non-hematological toxicity that does not resolve to ≤Grade 2 within 72 hours; excepting Grade 3 renal and hepatic toxicity which may take up to 7 days to resolve to ≤Grade 2
- Non-engraftment by Day 28 post-transplant

Component 2 monitoring guidelines for excessive toxicity (Stopping Rule events) occurring after the FT596 infusion based on Day 0 as the Transplant Day (ONLY POST FT596 EVENTS COUNT HERE):

- Mortality by Day 100
- Grade III-IV Acute GVHD by Day 100
- Any Grade 4 FT596 Infusion Related Reaction
- Any Grade 4 Dose Limiting Toxicity (DLT) event
- Grade 4 Lymphopenia (<200 cells/uL) at Day 100
- Engraftment failure by Day 28 (Component 2 only)

1 Objectives

1.1 Primary Objective

The primary objective of this study is:
Component 1: Establish a maximum tolerated dose (MTD) of FT596 when given 30 days after transplant and
Component 2: Confirm the MTD and safety of giving a single dose of FT596 at Day 7 post-transplant using one dose level below the MTD (MTD -1) or the MTD from Component 1.

1.2 Secondary Objectives

- To evaluate the adverse events related to FT596 administered post auto-HSCT in combination with rituximab (Rituxan or an FDA approved biosimilar, e.g. Truxima and Ruxience).
- To determine preliminary efficacy based on progression free survival (PFS) and relapse/progression at 12 months post auto-HSCT.
- To determine the incidence of non-relapse mortality at 100 days and 1 year post auto-HSCT.

1.3 Correlative Objectives

Correlative/exploratory objective include:

- To evaluate persistence of FT596 in blood after each FT596 infusion by immunophenotyping and PCR up to 1 year.
- To assess the association of FT596 cell persistence with safety and anti-tumor activity.
- To assess the association of baseline clinical and tumor characteristics with safety and response endpoints following administration of FT596.

2 Background and Significance

2.1 Introduction and Rationale for the Approach

Non-Hodgkin lymphoma (NHL) is the second most common hematologic malignancy. Diffuse large B cell lymphoma (DLBCL), the most common NHL subtype (30-40%), is an aggressive cancer that is rapidly fatal unless promptly treated. In the US, approximately 440,000 patients were treated for NHL in 2010 (SEER.gov). Although most patients initially achieve a remission, treatment fails for about 50% of patients. For these patient, Parma trial established the use of high-dose therapy (such as BEAM; BCNU, Etoposide, Cytarabine and Melphalan) with auto-HSCT as the standard of care. (Kondo 2016)

However relapse occurs frequently and estimated 5-year PFS rate is approximately 50-60%. (Vose 2013, Lerner 2007, Gisselbrecht 2012, Cuccuini 2012) Prospective trial compared Rituximab (R) BEAM vs ^{131}I-tositumomab BEAM to demonstrate similar PFS 48.6% (95% CI 38-58%) vs 47.9% (95% CI, 38.2% to 57%) at 2 years after auto-HSCT. Large multicenter CORAL study reported similar PFS of 52%. (Gisselbrecht 2012) Almost all relapses occur before 12 months post-HSCT. (Vose 2013, Lerner 2007, Gisselbrecht 2012, Hamadani 2014)

2.2 Determination of Cohort With High Risk of Post-HSCT Relapse

1. Lack of CR after front-line therapy and high International Prognostic Index (IPI) Score.

In the R-BEAM prospective trial, the only significant covariate in the multivariate model for PFS was disease status at the time of auto-HSCT. (Vose 2013) The patients in CR at auto-HSCT had an improved PFS compared with patients with a chemotherapy-sensitive persistent or relapsed lymphoma not in CR (HR 1.63; 95%CI 1.14-2.33). CORAL trial compared two salvage chemotherapy regimen in DLBCL and assessed the role of rituximab maintenance after auto-HSCT. Two factors associated with worse PFS were early relapse after front-line chemotherapy of < 12 months, and a secondary age-adjusted International Prognostic Index (IPI) score of 2-3. (Lerner 2007)

Center for International Blood and Marrow Transplantation Registry (CIBMTR) investigators recently analyzed outcomes after auto-HSCT and noted that patients with early failure (defined as primary induction failure and relapse <12 months from diagnoses) experienced relapse/progression rate of 47% (95% 41% to 52%) and PFS of 44% (95% CI, 38% to 50%) with 2-fold higher failure rate (P < .001) within first 9 months post auto-HSCT compared to patients with late treatment failure. (Hamadani 2014)

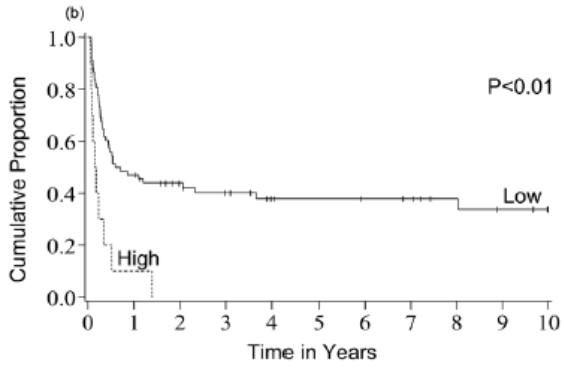


Figure 1. Progression free survival in DLCBL after autologous transplant in low and high risk groups defined by International Prognostic Index (IPI) at relapse

Data from our center demonstrated the median PFS of 2 months versus 8 months post auto-HSCT for the high- and low-risk IPI groups (total 80 patients). These findings support using the IPI assessed at relapse as a selection criterium to select patients who are treated with autologous transplantation for DLBCL in second complete or partial remissions. (Figure 1) (Lerner 2007).

2. *Alterations of c-myc gene is associated with poor PFS.*

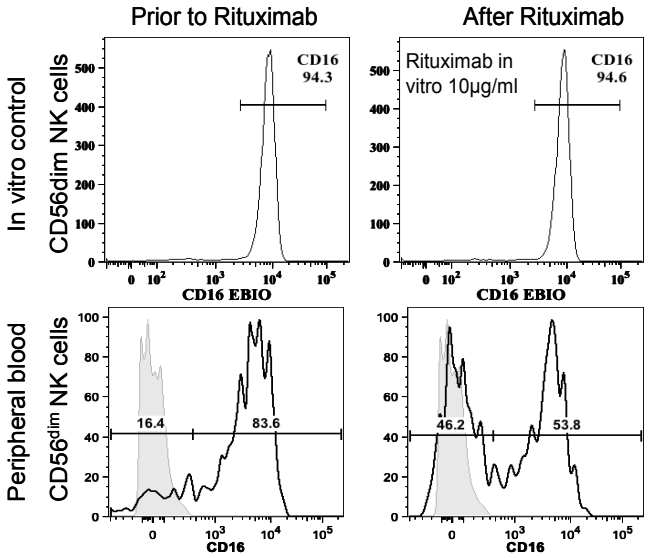
Approximately 5-10% of DLBCL harbor a 8q24/MYC rearrangement (MYC(+)). WHO now categorize this disease as aggressive B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements. CORAL study reported outcomes of 28 patients with MYC(+) rearrangement, targeted as either simple hit (25%) or complex hits (75%) including MYC/BCL2, MYC/BCL6, and MYC/BCL2/BCL6. (Cuccuini 2012) Compared to the MYC(-) DLBCL patients, the MYC(+) DLBCL patients presented with a more elevated LDH level and more advanced age adjusted IPI (P = .0039). The 4-year PFS in the MYC(+) DLBCL was 18%.

Another recent multicenter retrospective study examined the 331 DLBCL patients with primary induction failure in rituximab era defined as primary induction failure or relapse < 6 months from end of therapy. (Costa 2017) The presence of PIF, intermediate-high/high NCCN-IPI or MYC translocation predicted 2-year OS of 13.6% constituting ultra-high risk features. Our 132 patients who underwent autoHCT 2-year OS was 74.3%, 59.6% and 10.7% for patients with 0,1 and 2-3 ultra-high risk features respectively.

2.3 The Role of Rituximab Post-Transplant

Rituximab's key anti-cancer mechanism of action is mediated through FcγRIII (CD16) on NK cells; this receptor is by far the most potent NK activating receptor. Rituximab crosslinks CD16 and triggers vigorous production of cytokines and FT596 cell degranulation, leading to target cell killing (a process referred to as antibody-dependent cellular cytotoxicity; ADCC). Targeting CD20 on lymphoma cells with rituximab dramatically improves initial remission rates (by 10-20%), but resistance is common. The international CORAL study tested the impact of maintenance rituximab after autografting by evaluating DLBCL patients treated with rituximab or controls. (Gisselbrecht 2012) The 4-year event-free survival rates were identical in the two groups (52% and 53%). The limitations of rituximab efficacy may be due to decreased CD16 expression or poor NK cell function post transplantation. We hypothesize that FT596 engineering will enhance rituximab activity post-HCT.

CD16 expression is decreased after treatment with rituximab in vivo. In a control experiment (**Figure 2 top panel**), we incubated CD56^{dim} NK cells with rituximab (10 µg/ml) in vitro and showed that it does not block CD16 binding. We then tested peripheral blood from patients with DLBCL before and after the therapy with rituximab (375mg/m^2 x 4 doses). At baseline CD56^{dim} NK cells expressed high levels of CD16. After rituximab therapy, a large proportion of blood NK cells (46%) downregulated CD16 and became CD16 negative (**Figure 2, lower panel 16.4% vs 46.2%)**) demonstrating that rituximab treatment doses clip CD16 off NK cells in vivo.



The cellular product FT596 is rationally engineered to express a high-affinity non-cleavable CD16 receptor (hnCD16) to engage rituximab and mediate killing of DLBCL tumor cells which survived BEAM chemotherapy.

2.4 FT596

FT596 is an allogeneic NK cell immunotherapy produced from a clonal master human-induced pluripotent stem cell (iPSC) line engineered to express the following: a) a CD19-targeted CAR; b) a high-affinity non-cleavable CD16 receptor (hnCD16); and c) an IL-15/IL-15 receptor alpha fusion protein (IL-15RF) (Jing 2015; Li 2018). The clonal master cell bank (MCB) used for the production of FT596 was generated by selecting and expanding a single, well-characterized iPSC clone with defined transgene copy number and integration sites. The use of a clonal MCB as the starting material for routine Current Good Manufacturing Practices (cGMP) production of FT596 is intended to directly address many of the limitations associated with current patient- and donor-specific cell CD19-targeted CAR therapies.

Notably, many doses of FT596 drug product can be uniformly produced in a single manufacturing campaign. These doses of drug product are homogeneous and can be (i) tested to assure compliance with a pre-defined quality specification, (ii) cryopreserved in an infusion media, and (iii) stored to maintain a sustainable inventory. As such, in the clinical setting, FT596 has off-the-shelf availability for

potential use in multi-dose regimens in broad treatment populations, which may prove critical for driving long-term durable responses in patients with progressing disease.

The engineered features of FT596 are designed to result in greater potency and specificity against transformed B cells, and therefore, the potency of FT596 is expected to be superior to that of patients' endogenous NK cells. These features justify its investigation in B-cell malignancies:

- The cytotoxic effector function of FT596 is expected to be superior to that of patients' endogenous NK cells, which are diminished in number and poorly functional due to prior treatment regimens (e.g., chemotherapy) and disease-related immunosuppression.
- FT596 expresses a CD19-targeted CAR that has been specifically developed to support NK cell anti-tumor efficacy against CD19+ cells. Unlike CARs developed for T cells that include, for example, a CD28 co-stimulatory domain, FT596 CAR-mediated targeting is driven by NKG2D transmembrane and 2B4 co-stimulatory domains, which supports potent killing against CD19+ B cells. In nonclinical studies, CAR designs consisting of NKG2D transmembrane and 2B4 co-stimulatory domains outperformed a conventional CAR, consisting of CD28 and 41BB co-stimulatory domains, when expressed in NK cells (Li 2018).
- FT596 includes the expression of hnCD16 which consists of naturally occurring 158V polymorphism and an additional genetic alteration (S179P) that prevents cleavage of CD16. In clinical studies in patients whose endogenous NK cells express the high-affinity CD16 Fc receptor 158V variant, higher objective response rates (ORRs) and increased progression free-survival (PFS) were observed with treatment with rituximab, cetuximab, and trastuzumab (Cartron 2002; Bibeau 2009; Musolino 2008). In addition, the genetic alteration S179P prevents downregulation of CD16 upon activation due to cleavage of CD16 by the metalloproteinase ADAM17 (Jing 2015; Lajoie 2014), a mechanism that regulates NK cell activity (Romee 2013). Nonclinical studies conducted with cryopreserved FT596-R, the non-GMP research-use equivalent of FT596, demonstrated that the combination of FT596-R with the US Food and Drug Administration (FDA)-approved antibody-dependent cellular cytotoxicity (ADCC)-inducing monoclonal antibodies (mAbs), specifically rituximab, resulted in enhanced anti-tumor activity as compared to mAb alone, peripheral blood NK cells alone, or FT596 alone. Specifically, FT596-R in combination with rituximab demonstrated improved targeting of CD19+ CD20+ cancer cells, enhanced cytokine production, and enhanced combinatorial activity with chimeric antigen receptor targeting CD19 antigen. Based on these

observations, FT596 will be initially investigated in combination with the monoclonal ADCC-inducing antibodies targeting CD20, rituximab, and obinutuzumab, which are approved for the treatment of B-cell malignancies, and where CD19 loss or modification as a mechanism of resistance supports the targeting against a second tumor antigen expressed by the tumor B cells.

- FT596 expresses IL-15RF designed to provide an endogenous activation and proliferation signal, obviating the need for exogenous cytokine administration such as IL-2 and IL-15, which have been associated with significant toxicities that may limit clinical usage when incorporated into clinical studies of peripheral blood NK cells (Cooley 2019).
- Nonclinical evaluation of umbilical cord blood-derived NK cells engineered to express a CD19 CAR and secrete IL-15 demonstrated the feasibility of the overall approach of providing engineered NK cells for the treatment of B-cell malignancies, with clinical trials being planned (Liu 2018).

Overall, FT596 is expected to be uniform in composition, well-tolerated, available off-the-shelf for potential use in multi-dose treatment cycles, and to have improved anti-tumor activity through direct cytotoxicity, CAR-mediated targeting of CD19, as well as through ADCC in combination with mAbs for a unique dual-targeting approach. These features provide the rationale for the proposed Phase I study of a single dose of FT596 in combination with rituximab as relapse prophylaxis after an auto-HSCT for the treatment of aggressive B-cell and DBLCL lymphoma. If found safe, the next step will be to propose up to 3 doses of FT596 administered at Day 7, Day 30, and Day 60 post-transplant.

2.5 Study Rationale

There is an urgent need to develop well-tolerated and effective therapies to sustain remission in DLBCL post auto-HSCT.

Our hypothesis is that the FT596 will eliminate the chemotherapy resistant residual lymphoma cells which persist after high dose chemotherapy. The rationale to use FT596 post autoHCT is to harness the immune mediated anti-tumor killing at the time of minimal disease burden which is achieved by using high dose chemotherapy BEAM.

The rationale to initiate FT596 dose escalation portion at Day 30 is to allow patient recovery from toxicities of auto-HSCT and achieve stable blood count recovery. This timing is supported by our internal data which showed that median day of absolute neutrophil count (ANC) and platelet recovery occurred on days 10 and 19

after auto-HSCT. (Fair 2017) Day 30 is chosen to establish MTD and FT596 toxicity profile in transplant setting.

The rationale to move the FT596 infusion closer to Day 0 is to harness the lymphodepleting effect of BEAM chemotherapy. BEAM produce lymphopenia and endogenous release of IL-15 at the levels comparable to low dose fludarabine/cyclophosphamide. (Shi 2008, Porrata 2010) The presence of immunologic (homeostatic) environment post-HSCT was determined by elevated blood levels of IL-15 around day 7-10 post-transplant. (Shi 2008) In addition, BEAM chemotherapy triggered surge of IL-15 (blood levels at day 15: median 76.5pg/dl (range 5.4-219.2 pg/dl). (Porrata 2010) State of lymphopenia and endogenous cytokine surge early post-auto-HSCT may potentiate FT596 persistence in blood and in vivo expansion.

The rationale to combine FT596 with CD20 targeting monoclonal antibody rituximab is to mediate dual targeting of CD20 and CD19 to avoid antigen escape and increase anti-tumor efficacy. The treatment goal is to eliminate chemoresistant lymphoma cells after autoHCT and improve 1-year PFS from 50% to 75%.

3 Study Design

This is a Phase I multi-center study to evaluate the safety of a single dose of FT596 when given with rituximab as relapse prevention in patients who have undergone an autologous hematopoietic stem cell transplant (auto-HSCT) for diffuse large or high-grade B cell lymphoma.

This study is presented to the patient and consent is signed at the time consent for the autologous transplant is obtained. Research related samples are collected prior to the start of conditioning on any consented patient. Alternatively, a patient also may be consented, screened, and enrolled after the transplant provided the patient can begin treatment within the assigned window.

The transplant procedures and follow-up are conducted per institutional standard of care. Participation in this study does not affect or impact the transplant, supportive care, and subsequent post-transplant care, except that, if post-transplant radiation therapy is planned, it must be delayed until after Day 100.

FT596 is comprised of allogeneic natural killer (NK) cells expressing a CD19-targeted chimeric antigen receptor (CAR), a high-affinity non cleavable CD16 receptor (hnCD16), and an interleukin (IL)-15/IL-15 receptor alpha fusion protein (IL-15RF). FT596 is expected to be uniform in composition, available off the shelf

for use in a multi dose treatment plan. The mechanism of action is targeting B-cell tumor cells through direct cytotoxicity, CAR-mediated targeting of CD19 as well as through antibody-dependent cellular cytotoxicity (ADCC) in combination with rituximab for a dual-targeting approach.

This study uses a single dose of the investigational product FT596 in the early post-transplant period. Rituximab (Rituxan or an FDA approved biosimilar, e.g. Truxima and Ruxience) is given 48 to 72 hours prior to FT596. The goal of this study is to 1) establish a maximum tolerated dose (MTD) of FT596 when given 30 days after transplant and 2) to confirm the MTD and safety of giving a single dose of FT596 at Day 7 post-transplant starting at one dose level below the MTD identified at Day 30.

Component 1: Identify the maximum tolerated dose (MTD) of FT596 when given as a single dose at Day 30.

Up to three FT596 dose levels are planned for administration on Day 30: Dose Level 1: $9x10^7$ cells/dose, Dose Level 2: $3x10^8$ cells/dose, Dose Level 3: $9x10^8$ cells/dose with a Dose Level -1: $3x10^7$ cells/dose tested only if DLT at DL1.The maximum tolerated dose will be determined by using a modified continual reassessment method (CRM).

Patients are enrolled in cohorts of 3 starting at Dose Level 1. A minimum of 28 days will separate each cohort. For Dose Level 1 a minimum of 28 days will separate each patient to assess for dose limiting toxicity (DLT). In subsequent cohorts, the 1st and 2nd patient will be separated by at least 28 days and at least 14 days will separate the 2nd and 3rd patient.

Each new cohort of three patients will be sequentially assigned to the most appropriate dose based on the updated toxicity probabilities under the continuous reassessment method (CRM), and the MTD will be identified when the total sample size of 18 is exhausted or 6 patients are sequentially enrolled at the same dose.

Definitions of dose limiting toxicity and monitoring for excessive toxicity are found in Section 12.4.

Component 2: To determine the safety of FT596 when given at Day 7 based on the MTD from Component 1.

NOTE: Component 2 may not begin until after the FDA gives permission to proceed (refer to Section 6.3).

Component 2 will use a similar design but identifies the MTD of FT596 when given as a single dose at Day 7 post-transplant. Up to two dose levels of FT596 are planned (one dose level below the MTD from Component 1 and the MTD from Component 1). Any two sequential dose levels of FT596 may be included: Dose Level -1: $3x10^7$ cells/dose, Dose Level 1: $9x10^7$ cells/dose, Dose Level 2: $3x10^8$ cells/dose, Dose Level 3: $9x10^8$ cells/dose.

The maximum tolerated dose will be determined by using a modified continual reassessment method (CRM). Patients are enrolled in cohorts of 3 starting at one dose level below the MTD of Component 1 (MTD-1). Only the MTD-1 and the MTD of Component 1 will be tested. A minimum of 28 days will separate each cohort. For the 1st cohort a minimum of 28 days will separate each patient to assess for dose limiting toxicity (DLT). In subsequent cohorts, the 1st and 2nd patient will be separated by at least 28 days and at least 14 days will separate the 2nd and 3rd patient. Each new cohort of three patients will be sequentially assigned to the most appropriate dose based on the updated toxicity probabilities. The MTD will be identified when the total sample size of 18 is exhausted or 6 patients are sequentially enrolled at the same dose.

Definitions of dose limiting toxicity and monitoring for excessive toxicity are found in Section 12. 4.

Follow-up (all patients): Direct study participation ends at 1 year post-transplant.

Long-Term Follow-Up (any patient who received at least one dose of FT596): After 1 year, follow-up will transfer to a separate long-term follow-up (LTFU) study (UMN CPRC #2020LS052) to continue the FDA's required 15 year follow-up after treatment with a genetically modified cell therapy. Participation in the LTFU study is mandatory as part of the inclusion criteria of this treatment study.

4 Patient Selection

Study entry is open to adults 18 years and older regardless of gender, race or ethnic background. While there will be every effort to seek out and include females and minority patients, the patient population is expected to be no different than those adults undergoing an autologous transplant for non-Hodgkin lymphoma at the participating institutions.

4.1 Inclusion Criteria

- Diagnosis of diffuse large B cell lymphoma or aggressive (high grade) B-cell lymphoma for which an autologous stem cell transplant is planned or recently completed
- High risk for relapse defined as at least one of the below:
  - Primary induction failure (no complete or partial remission at any point after diagnosis
  - Initial remission duration < 12 months
  - Lack of complete metabolic (PET scan) response after 2-3 cycles of salvage chemotherapy
  - Evidence of c-myc and bcl-2 and/or bcl-6 re-arrangement (double hit or triple hit lymphoma)
  - Age-adjusted International Prognostic Index (IPI) 2-3 at relapse
- Age 18 years or older at the time of signing consent.
- Agrees to use adequate contraception (or evidence of sterility) for at least 12 months after the last dose of rituximab.
- Agrees and signs the separate consent for up to 15 years of long-term follow-up study
- Provide voluntary written consent prior to the performance of any research related activities.

4.2 Exclusion Criteria

- Receipt of any investigational therapy within 28 days prior to the first dose of FT596 or planned use of an investigational therapy during the first 100 days after transplant
- Planned post-transplant irradiation prior to Day +100
- Seropositive for HIV
- Active Hepatitis B or C infection with detectable viral load by PCR
- Body weight <50kg
- Known allergy to the following FT596 components: albumin (human) or DMSO
- Unable to receive rituximab

4.3 Confirmation of Continuing Eligibility Post-Transplant

- No life-threatening medical issues (i.e. ongoing Grade 4 adverse events) where, in the opinion of the treating investigator, use of FT596 is not in the patient's best interest.
- No active uncontrolled infection
- Adequate organ function post-transplant including:
  - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤5 x ULN (Grade 2 CTCAE v5)
  - total bilirubin ≤1.5 x ULN (Grade 1 CTCAE v5)
  - serum creatinine ≤1.5 x ULN (Grade 1 CTCAE v5)
  - oxygen saturation ≥93% on room air
- **For Day 30 dosing only** – CBC requirement consistent with engraftment (ANC>500, platelet>20,000 without transfusion support within previous 7 days). There are no CBC parameters for Day 7 dosing.
- No requirement for systemic immunosuppressive therapy (> 5mg prednisone daily) during the FT596 dosing period.

FT596 may be delayed for up to 3 days for these events to resolve.

5 Patient Screening and Enrollment

For the majority of participants, consent for this study will be presented as part of the pre-transplant discussion as research related samples are collected before beginning of conditioning chemotherapy.

Alternatively, a patient also may be consented and enrolled after transplant provided the patient 1) can begin treatment within their assigned window, 2) they meet all of the inclusion criteria and none of the exclusion criteria based on the previously documented standard of care pre-transplant assessment and 3) meet the post-transplant requirements found in Section 4.3. Research related procedures and sample collections missed due to late consenting are not protocol deviations.

5.1 Registration with the University of Minnesota Clinical Trials Office

Any patient who is consented is to be registered in OnCore by the site Study Coordinator or designee.

If a patient is consented but is not enrolled in the study treatment (i.e. is found to be ineligible based on pre-transplant inclusion/exclusion criteria), the patient's record is updated in OnCore as a screen failure and reason for exclusion recorded.

Additional information is found in the study's Procedures Manual for Participating Sites.

In addition, participating institutions are responsible for fulfilling any local study registration requirements.

5.2 Patient Enrollment to Study Treatment in OnCore

To be eligible for study treatment, the patient must sign the treatment consent and meet each inclusion criteria and none of the exclusion criteria on the eligibility checklist based on an eligibility assessment documented in the patient's medical record.

After transplant, the study doctor will need to assess the patient to determine if the criteria in Section 4.3 is met and continuing on the study is in the best interest of the patient based on their current medical situation.

The patient is assigned to the currently enrolling treatment plan after the transplant and confirmation of continuing eligibility.

5.3 Patients Who Do Not Begin Study Treatment

If a patient is enrolled in the study (i.e. assigned a sequence number) and is later found unable to begin FT596, the patient will be removed from study and treated at the physician's discretion. The study staff will update OnCore of the patient's non-treatment status (off study) with the reason for removal from study prior to starting study treatment clearly indicated. The patient will be replaced to complete enrollment. Any data and research samples collected up to this point will be retained as detailed in the written consent document.

If a patient receives FT596, they are considered on treatment and most continue follow-up per Section 8.

6 Treatment Plan

Primary supportive care is to continue according to the primary transplant protocol. In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy (i.e. acetaminophen, diphenhydramine, antimicrobials, etc.).

Because they may inhibit NK cell function, systemic corticosteroids should be avoided during the treatment period (3 days before and through 14 days after FT596) unless absolutely required. Intravenous glucocorticoid as premedication for rituximab may be administered per the USPI or institutional guidelines. Methylprednisolone should be used as preferred glucocorticoid premedication given its shorter half-life.

Treatment may be given as an inpatient or an outpatient. There is no protocol driven requirement for hospitalization.

For scheduling purposes, the rituximab/FT596 "package" is administered with a +3 day window from the targeted FT596 administration day (Day 30 or Day 7). Rituximab or an FDA approved biosimilar is given 2-3 days (48 to 72 hours) prior to the planned FT596 infusion.

6.1 Rituximab or an FDA Approved Biosimilar and FT596 Administration General Guidelines

Rituximab or an FDA approved biosimilar and FT596 are administered in the same manner regardless of FT596 dose and the administration days. Refer to the following sections for detailed information including enrollment plan, definition of dose limiting toxicity and early study stopping events.

- **Section 6.2 – Component 1:** Identify FT596 MTD when given on Day 30 only.
- **Section 6.3 – Component 2:** Determine the MTD and safety of Day 7 FT596.

6.1.1 Rituximab or FDA Approved Biosimilar (2-3 days prior to each FT596 Administration)

Rituximab (Rituxan or an FDA approved biosimilar, e.g. Truxima and Ruxience) 375 mg/m^2 is administered as an IV infusion per institutional practice and the specific product's package insert on 2-3 days (48 to 72 hours) prior to the FT596. Pre-medications and supportive care per institutional standard of care guidelines.

6.1.2 FT596 Administration

FT596 is given 2-3 days after rituximab; however, it may be delayed for up to 7 days until all rituximab infusion related toxicities resolve to ≤Grade 1.

FT596 Thawing Overview: FT596 is provided in one or more cryopreserved bags based on the patient's dose level. The correct number of bags are transferred to the site of infusion using a validated cooler. Thawing occurs on the unit just prior to administration. When dose level requires multiple bags, bags are thawed sequentially. FT596 is stable for up to 60 minutes post-thaw. Administration of the cell product must begin within 60 minutes of thawing.

FT596 Infusion guidelines: FT596 must be administered via gravity using a Fate approved IV administration set with an in-line filter. Total infusion time per bag is less than 10 minutes. If multiple bags are used, a short delay between infusions occur to allow for product thawing. To infusion 3 bags of cells (the maximum required for the dose levels in this study), total infusion time from the start of the 1st bag to the end of the last bag would be 30-40 minutes.

Complete information is provided in the FT596 Storage, Handling, and Administration Guidance

The end of administration time should be recorded after the rinse step has been completed. When the study drug administration has been completed, discard the empty study drug bag/tubing in accordance with local site policy.

Pre-Medications: Prior to administration of FT596 and 4-6 hours later, patients should be pre-medicated with acetaminophen 650 mg orally (PO) and diphenhydramine 25 PO. Corticosteroids should not be used as pre-medication for FT596.

Vital Signs: Vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiration rate) are performed in association with the FT596 infusion at the following time points: within 15 minutes of the infusion start, at 10 (±5) minutes during infusion, and every 15 (±5) minutes for 1 hour after the end of the last administered bag of FT596.

Collection of research sample 30 (±5) minutes after the last bag of FT596 is infused per Section 8.2. One or more bags are given depending on the dose level.

Monitoring for Infusion Related Reactions: All patients are monitored for signs of an infusion related reaction. The highest grade infusion reaction for the FT596 infusion must be documented (and if applicable reported as a dose limiting toxicity and/or an SAE).

Refer to Section 7.1 for the management of any grade of an infusion related reaction.

If a Grade 3 or 4 infusion related reaction occurs (defined as CTCAE v 5.0 – prolonged or life-threatening consequences), the infusion is stopped if possible (i.e. no additional bags of cells are given) and the patient receive supportive care per Section 7.1 guidelines. The patient will receive no further FT596.
All patients are monitored for adverse events, dose limiting toxicity and death per Section 10.Refer to Section 7 for management of FT596 related toxicity.

6.2 Component 1: Identify FT596 MTD When Given on Day 30 Only

In Component 1, all patients will receive a single dose of FT596 on Day 30 (+3 days) post-transplant. Rituximab (Rituxan or an FDA approved biosimilar, e.g. Truxima and Ruxience) 375 mg/m^2 is administered 2-3 days prior to FT596.

Up to three FT596 dose levels are planned: Dose Level 1: 9x10^7 cells/dose, Dose Level 2: 3x10^8 cells/dose, Dose Level 3: 9x10^8 cells/dose with a Dose Level -1: 3x10^7 cells/dose tested only if DLT at DL1. Refer to Section 3 regarding the required staggering of enrollment.

Dose limiting toxicity for Component 1 is defined as:
Component 1 dose limiting toxicity is defined as any of the following events within 28 days after the FT596 dosing based on CTCAE v5:

- Grade 4 hematologic toxicity lasting > 7 days (not including lymphopenia)
- Grade 4 non-hematologic toxicity
- Grade ≥3 FT596 Infusion Related Reaction
- Grade 2 acute GVHD that requires steroid therapy >7 days or progression after 3 days of steroids or has partial response after 14 days of treatment
- Grade ≥3 acute GVHD
- Grade 4 cytokine release syndrome (CRS)
- Grade 3 CRS that does not resolve to < Grade 2 in 72 hours
- Grade 3 neurotoxicity
- Grade 3 organ toxicity involving vital organs; cardiac, central nervous system and pulmonary that lasts longer than 7 days including Grade 3 Investigations (laboratory values) of any duration that indicate damage to vital organs.
- Any Grade 3 non-hematological toxicity that does not resolve to ≤Grade 2 within 72 hours; excepting Grade 3 renal and hepatic toxicity which may take up to 7 days to resolve to ≤Grade 2

6.3 Component 2: Safety of FT596 when given at Day 7 based on the MTD from Component 1

Prior to the start of enrollment in Component 2, a summary of patient data from Component 1 will be submitted to the FDA for their review. Included in this report will be enrollment and treatment information, a summary of adverse events, DLT's SR events and SAEs as well as any disease status information. Component 2 may proceed if permission is received from the FDA. Otherwise the study will stop.
In Component 2, all patients will receive a single dose of FT596 on Day 7 (+3 days) post-transplant. Rituximab (Rituxan or an FDA approved biosimilar, e.g. Truxima and Ruxience) 375 mg/m^2 is administered 2-3 days prior to FT596.

Up to two dose levels of FT596 are planned (one dose level below the MTD from Component 1 and the MTD from Component 1). Any two sequential dose levels of FT596 may be included: Dose Level -1: $3x10^7$ cells/dose, Dose Level 1: $9x10^7$ cells/dose, Dose Level 2: $3x10^8$ cells/dose, Dose Level 3: $9x10^8$ cells/dose. Refer to Section 3 regarding the required staggering of enrollment.

Dose limiting toxicity for Component 2 is defined as:
Component 1 dose limiting toxicity is defined any of the following events within 28 days after the FT596 dosing based on CTCAE v5:

- Grade 4 hematologic toxicity lasting > 7 days (not including lymphopenia)
- Grade 4 non-hematologic toxicity
- Grade ≥3 FT596 Infusion Related Reaction
- Grade 2 acute GVHD that requires steroid therapy >7 days or progression after 3 days of steroids or has partial response after 14 days of treatment
- Grade ≥3 acute GVHD
- Grade 4 cytokine release syndrome (CRS)
- Grade 3 CRS that does not resolve to < Grade 2 in 72 hours
- Grade 3 neurotoxicity
- Grade 3 organ toxicity involving vital organs; cardiac, central nervous system and pulmonary that lasts longer than 7 days including Grade 3 Investigations (laboratory values) of any duration that indicate damage to vital organs.
- Any Grade 3 non-hematological toxicity that does not resolve to ≤Grade 2 within 72 hours; excepting Grade 3 renal and hepatic toxicity which may take up to 7 days to resolve to ≤Grade 2
- Non-engraftment by Day 28 post-transplant

6.4 Monitoring for Excessive Toxicity (Component 1 and Component 2)

Each component will be monitored independently for the following events of excessive toxicity occurring after the FT596 infusion based on Day 0 as the Transplant Day (ONLY POST FT596 EVENTS COUNT HERE) per Section 12.4

- Mortality by Day 100
- Grade III-IV Acute GVHD by Day 100
- Any Grade 4 FT596 Infusion Related Reaction
- Any Grade 4 Dose Limiting Toxicity (DLT) event
- Grade 4 Lymphopenia (<200 cells/uL) at Day 100
- Engraftment failure by Day 28 (Component 2 only)

6.5 Permitted and Prohibited Concomitant Medications/Therapies

Primary supportive care is to continue according to the primary transplant protocol. In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy (i.e. acetaminophen, diphenhydramine, antimicrobials, etc.).

Because they may inhibit NK cell function, systemic corticosteroids should be avoided during the treatment period (3 days before the first FT596 through 14 days after) unless absolutely required. Intravenous glucocorticoid as premedication for rituximab may be administered per the USPI or institutional guidelines. Methylprednisolone should be used as preferred glucocorticoid premedication given its shorter half-life.

Glucocorticoids should not be used as premedication for FT596.

6.6 Duration of Treatment

Treatment consists of a single dose of rituximab or an FDA approved biosimilar followed 2-3 days later by FT596 at the patient's assigned dose/schedule. If a patient cannot receive FT596 by 7 days after rituximab due to unresolved infusion related toxicity (refer to Section 6.1), FT596 is not given.

All patients receiving at least one dose of FT596 will be followed per Section 8.1.

6.7 Duration of Study Participation

Follow-up for disease and survival endpoints continues through 1 year post-transplant.

Direct study participation ends approximately 30 days after the last FT596 infusion and once an End of Treatment visit has occurred.

Clinical information including disease status and potential late toxicities associated with FT596 will be abstracted from follow-up visits associated with the transplant at Day 100, Day 180, Day 270 (if done), and Day 365. After Day 365 (1 year), the patient's follow-up will transfer to a designated long-term follow-up protocol per Section 6.8.

Rituximab or the FDA approved biosimilar may continue (independent of this study) per institutional practice.

6.8 Continuation of Follow-Up via a Separate Long-Term Follow-Up Protocol

FT596 is an engineered cellular immunotherapy product and the long-term safety risk is not known and may include conditions with delayed onset relative to FT596 administration. Specific conditions potentially related to engineered cellular immunotherapy products such as FT596, including but not limited to, new malignancies, new or worsening neurologic disorders, new or worsening autoimmune or rheumatologic disorder, or new hematologic disorder will be documented and reported to the FDA as part of IND the annual report.

At the end of the follow-up period for this study, follow-up for up to 15 years from the first FT596 cell infusion will continue on a separate long-term follow-up (LTFU) study (UMN CPRC#2020LS052). Consent to the LTFU study is obtained at the time of consent for the treatment study.

7 Management of Potential Toxicities Associated FT596

No FT596 clinical data are available.

The long-term safety risk is not known and may include conditions with delayed onset relative to FT596 administration.

The information provided below is extrapolated from other NK cell products and other cell products in general.

All adverse events will be defined and graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

7.1 Infusion Related Reaction Associated with FT596

Patients will be observed for the occurrence of acute allergic/anaphylactoid infusion reactions such as rigors and chills, rash, urticaria, hypotension, dyspnea, and angioedema during and after the infusion.

The management of acute infusion or allergic reactions that occur during FT596 administration is described below.

If Grade 4 Infusion-Related Reaction (Life-threatening consequences; urgent intervention indicated):

Stop FT596 administration. Do not restart.

The volume of FT596 administered prior to the infusion-related reaction must be documented; retain any remaining product and contact Dr. Bachanova or designee for further instructions.

If Grade ≤3 Infusion-Related Reaction (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae):

- Interrupt FT596 administration.
- Manage symptoms, e.g., with antihistamines, antipyretics and analgesics, according to standard institutional practice standards.
- Resume FT596 administration only upon complete resolution of the infusion-related reaction and at the discretion of the Investigator. Given that FT596 administration may involve single or multiple bags depending on the total planned dose and accounting for the stability of FT596 post-thaw, FT596 administration may continue following resolution to a Grade 1 infusion-related reactions as follows:

  <u>If single-bag FT596 dosing:</u>

  - No additional FT596 may be administered.
  - The volume of FT596 administered prior to the infusion-related reaction must be documented; retain any remaining product and contact the Study PI (or designee) for further instruction.
  - Additional bags may not be administered to make up for FT596 that was not administered from the bag during which the infusion-related reaction occurred.

If multiple-bag FT596 dosing:

- The volume of FT596 administered from the bag during which the infusion-related reaction occurred must be documented; retain any remaining product from the bag and contact the Sponsor for further instruction.
- If dosing with additional FT596 bags was planned, they may be thawed and administered.
- Additional bags beyond what was originally planned may not be administered to make up for FT596 that was not administered from the bag during which the infusion-related reaction occurred.

7.2 DMSO Related Risks

FT596 is formulated in DMSO to enable cryopreservation. DMSO side effects and symptoms are generally associated with histamine release and include coughing, flushing, rash, chest tightness and wheezing, nausea and vomiting, and cardiovascular instability. Treat by slowing the rate of infusion, medicating with antihistamines, and treating symptoms per institutional practice. Recommended patients receive IV hydration with normal saline (NS) 250 ml bolus before and 250 ml bolus after FT596 administration to reduce the potential risks associated with DMSO.

7.3 Cytokine Release Syndrome (CRS) or CRS-Like Symptoms

While CRS is a clearly defined syndrome with T-cell therapy, it is generally not believed to be a toxicity associated with NK cell therapies unless administered with cytokines that may independently drive the proliferation and activation of CD8+ T cells, e.g., exogenous IL-15 (Cooley 2019).

If CRS is suspected, CRP and ferritin levels should be assessed locally, and a research related serum sample should be collected for an IL-6 level (if feasible).

CRS must be graded as outlined in the ASTCT CRS consensus grading system per Section 10 (Lee 2019).

If CRS occurs (e.g. a differential diagnosis is recorded in the institutional medical record), CRP and ferritin levels should be done three times weekly until the resolution of CRS per Section 8.1. In addition, a research related serum sample should be collected for an IL-6 level at the time of any change (increase or decrease) in the CRS grade. Because patients may be outpatients any missed collection time points will not be a protocol deviations.

Management of CRS should follow the recommended management algorithm provided in Table 1 (Neelapu 2018) and/or institutional practice.

Table 1: Recommendations for the Management of Cytokine Release Syndrome

Grade	Sign/Symptom	Management
Grade 1	Fever or organ toxicity	• Acetaminophen and hypothermia blanket for the treatment of fever • Ibuprofen can be used as second treatment option for fever, if not contraindicated • Assess for infection using blood and urine cultures, and chest radiography • Empiric broad-spectrum antibiotics and filgrastim if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of constitutional symptoms and organ toxicities • Consider tocilizumab 8 mg/kg [a] IV or siltuximab 11 mg/kg IV for persistent (lasting ≥3 days) and refractory fever
Grade 2	Hypotension	• IV fluid bolus of 500–1,000 mL of normal saline • Can give a second IV fluid bolus if systolic blood pressure remains <90 mmHg • Tocilizumab 8 mg/kg [a] IV or siltuximab 11 mg/kg IV for the treatment of hypotension that is refractory to fluid boluses; up to 3 additional doses of tocilizumab may be administered, and the interval between consecutive doses should be at least 8 hours. • If hypotension persists after two fluid boluses and anti-IL-6 therapy, start vasopressors, consider transfer to ICU, obtain echocardiogram, and initiate other methods of hemodynamic monitoring • In subjects at high-risk [b] or if hypotension persists after 1–2 doses of anti-IL-6 therapy, dexamethasone can be used at 10 mg IV every 6 hours • Manage fever and constitutional symptoms as in Grade 1
	Hypoxia	• Supplemental oxygen • Tocilizumab or siltuximab ± corticosteroids and supportive care, as recommended for the management of hypotension
	Organ toxicity	• Symptomatic management of organ toxicities, as per standard guidelines • Tocilizumab or siltuximab ± corticosteroids and supportive care, as indicated for hypotension
Grade 3	Hypotension	• IV fluid boluses as needed, as recommended for the treatment of Grade 2 CRS • Tocilizumab and siltuximab as recommended for Grade 2 CRS, if not administered previously • Vasopressors as needed • Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring as in the management of Grade 2 CRS • Dexamethasone 10 mg IV every 6 hours; if refractory, increase to 20 mg IV every 6 hours

Table 1: Recommendations for the Management of Cytokine Release Syndrome		
Grade	Sign/Symptom	Management
		• Manage fever and constitutional symptoms as indicated for Grade 1 CRS
	Hypoxia	• Supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation • Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above
	Organ toxicity	• Symptomatic management of organ toxicities as per standard guidelines • Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above
Grade 4	Hypotension	• IV fluids, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring as defined for the management of Grade 3 CRS • Methylprednisolone 1 g/day IV • Manage fever and constitutional symptoms as in Grade 1 CRS
	Hypoxia	• Mechanical ventilation • Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above
	Organ toxicity	• Symptomatic management of organ toxicities as per standard guidelines • Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above

CRS, cytokine release syndrome; ICU, intensive care unit; IV, intravenous.

NOTE: All medication doses indicated are for adults.

[a] Maximum amount of tocilizumab per dose is 800 mg.

[b] High-risk subjects include those with bulky disease and those with comorbidities.

Reference: Neelapu 2018., Actemra USPI

7.4 Neurotoxicity

While CNS toxicity is a clearly defined syndrome associated with T-cell-based therapies, it is rare and generally not believed to be a toxicity associated with NK cell therapies. Neurotoxicity was reported in one trial of adoptively transferred NK cells given with subcutaneous IL-15 but the mechanism of the toxicity was not well defined (Cooley 2019). Nervous system toxicities following CD19 CAR-T therapy is characterized by encephalopathy, confusion, delirium, aphasia, obtundation, and seizures (Yescarta USPI 2017; Kymriah USPI 2018). Cases of cerebral edema have also been reported (Brudno 2016).

If signs and symptoms of CNS toxicity occurs, it will be graded as outlined in the ASTCT consensus grading system for ICANS (Lee 2019, Section 10); management should follow current recommendations for CAR-T-cell therapies (Neelapu 2018).

If the patient develops neurological toxicity for which cerebrospinal fluid (CSF) analysis is performed, in addition to standard clinical testing, the sample will be tested for Human Herpes Virus (HHV 6&7) since HHV6 and HHV-7 may cause

neurological toxicity in an immunocompromised host which may go unrecognized. In addition, quantitative testing in blood for HHV6 and HHV7 in the context of neurotoxicity will be done. Neurotoxicity must be monitored as per the Section 8.1 using the ASTCT guidelines for grading ICANS (Section 10) based on the immune cell-associated encephalopathy (ICE) score. Determinants of the ICE score are outlined below.

ICE Score Determination:

- **Orientation:** Orientation to year, month, city, hospital: 1 point each for maximum of 4 points
- **Naming:** Name 3 objects (e.g., point to clock, pen, button): 1 point each for maximum of 3 points
- **Following commands:** (e.g., show me 2 fingers or close your eyes and stick out your tongue): 1 point
- **Writing:** Ability to write a standard sentence (e.g., our national bird is the bald eagle): 1 point
- **Attention:** Count backwards from 100 by ten: 1 point

Table 2 ASTCT Immune Effector Cell-Associated Neurotoxicity Syndrome Grading [a]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score [b]	7–9	3–6	0–2	0 (subject is unarousable and unable to perform ICE.)
Depressed level of consciousness [c]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subjects is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
Seizure	N/A	N/A	Any clinical seizure Focal/generalized that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 minutes); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor Findings [d]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis

Table 2 ASTCT Immune Effector Cell-Associated Neurotoxicity Syndrome Grading [a]				
Neurotoxicity Domain	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Raised ICP/ Cerebral Edema	N/A	N/A	Focal/local edema on neuroimaging [e]	Diffuse cerebral edema on neuroimaging; Decerebrate or Decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ASTCT, American Society for Transplantation and Cellular Therapy; CTCAE, Common Terminology Criteria for Adverse Events; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; ICP, intracranial pressure; EEG, electroencephalogram; N/A, not applicable.

[a] ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause. For example, a subject with an ICE score of 3 who has a generalized seizure is classified as having Grade 3 ICANS.

[b] A subject with an ICE score of 0 may be classified as having Grade 3 ICANS if the subject is awake with global aphasia. But a subject with an ICE score of 0 may be classified as having Grade 4 ICANS if the subject is unarousable.

[c] Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication).

[d] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0 but they do not influence ICANS grading.

[e] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Reference: Lee 2019.

Management of clinical neurotoxicity, i.e., encephalopathy syndrome, status epilepticus, and raised intracranial pressure, should follow current recommendations for CAR-T-cell therapies (Neelapu 2018; Table 3, Table 4, and Table 5) and/or institutional practice.

Table 3 Recommendations for the Management of Encephalopathy Syndrome	
Grade	**Management**
Grade 1	• Vigilant supportive care; aspiration precautions; IV hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing • Convert all oral medications and/or nutrition to IV if swallowing is impaired • Avoid medications that cause central nervous system depression • Low doses of lorazepam (0.25–0.5 mg IV every 8 hours) or haloperidol (0.5 mg IV every 6 hours) can be used, with careful monitoring, for agitated subjects • Neurology consultation • Fundoscopic exam to assess for papilloedema • MRI of the brain with and without contrast; diagnostic lumbar puncture with measurement of opening pressure; MRI spine if the subject has focal peripheral neurological deficits; CT scan of the brain can be performed if MRI of the brain is not feasible • Daily 30-minute EEG until toxicity symptoms resolve; if no seizures are detected on EEG, continue levetiracetam 750 mg every 12 hours • If EEG shows non-convulsive status epilepticus, treat as per algorithm in Table 4 • Consider anti-IL-6 therapy with tocilizumab 8 mg/kg [a] IV or siltuximab 11 mg/kg IV, if encephalopathy is associated with concurrent CRS
Grade 2	• Supportive care and neurological work-up as described for grade 1 encephalopathy • Tocilizumab 8 mg/kg [a] IV or siltuximab 11 mg/kg IV if associated with concurrent CRS • Dexamethasone 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours if refractory to anti-IL-6 therapy, or for encephalopathy without concurrent CRS

Table 3 Recommendations for the Management of Encephalopathy Syndrome	
Grade	**Management**
	• Consider transferring subject to ICU if encephalopathy associated with Grade ≥2 CRS
Grade 3	• Supportive care and neurological work-up as indicated for Grade 1 encephalopathy • ICU transfer is recommended • Anti-IL-6 therapy if associated with concurrent CRS, as described for Grade 2 encephalopathy and if not administered previously • Corticosteroids as outlined for Grade 2 encephalopathy if symptoms worsen despite anti-IL-6 therapy, or for encephalopathy without concurrent CRS; continue corticosteroids until improvement to Grade 1 encephalopathy and then taper • Stage 1 or 2 papilloedema with CSF opening pressure <20 mmHg should be treated as per algorithm presented in Table 4 • Consider repeat neuroimaging (CT or MRI) every 2–3 days if subject has persistent grade ≥3 encephalopathy
Grade 4	• Supportive care and neurological work-up as outlined for Grade 1 encephalopathy • ICU monitoring; consider mechanical ventilation for airway protection • Anti-IL-6 therapy and repeat neuroimaging as described for Grade 3 encephalopathy • High-dose corticosteroids continued until improvement to Grade 1 encephalopathy and then taper; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days • For convulsive status epilepticus, treat as per algorithm in Table 4 • Stage ≥3 papilloedema, with a CSF opening pressure ≥20 mmHg or cerebral oedema, should be treated as per algorithm in Table 4

CAR, chimeric antigen receptor; CSF, cerebrospinal fluid; CRS, cytokine release syndrome; CT, computed tomography (scan); EEG, electroencephalogram; ICU, intensive care unit; IV, intravenous; MRI, magnetic resonance imaging.
[a] Maximum amount of tocilizumab per dose is 800 mg.
Reference: Neelapu 2018.

Table 4 Recommendations for the Management of Status Epilepticus	
Status Epilepticus Type	**Management**
Non-convulsive status epilepticus	• Assess airway, breathing, and circulation; check blood glucose • Lorazepam [a] 0.5 mg IV, with additional 0.5 mg IV every 5 minutes, as needed, up to a total of 2 mg to control electrographical seizures • Levetiracetam 500 mg IV bolus, as well as maintenance doses • If seizures persist, transfer to ICU and treat with phenobarbital loading dose of 60 mg IV • Maintenance doses after resolution of non-convulsive status epilepticus are as follows: lorazepam 0.5 mg IV every 8 hours for three doses; levetiracetam 1,000 mg IV every 12 hours; phenobarbital 30 mg IV every 12 hours
Convulsive status epilepticus	• Assess airway, breathing, and circulation; check blood glucose • Transfer to ICU • Lorazepam [a] 2 mg IV, with additional 2 mg IV to a total of 4 mg to control seizures • Levetiracetam 500 mg IV bolus, as well as maintenance doses

Table 4 Recommendations for the Management of Status Epilepticus	
Status Epilepticus Type	**Management**
	• If seizures persist, add phenobarbital treatment at a loading dose of 15 mg/kg IV • Maintenance doses after resolution of convulsive status epilepticus are: lorazepam 0.5 mg IV every 8 hours for three doses; levetiracetam 1,000 mg IV every 12 hours; phenobarbital 1–3 mg/kg IV every 12 hours • Continuous electroencephalogram monitoring should be performed, if seizures are refractory to treatment

ICU, intensive care unit; IV, intravenous.
NOTE: All indicated doses of medication are for adult subjects.
[a] Lorazepam is the recommended benzodiazepine because it is short-acting, compared with diazepam, and has been widely used in the management of seizures.
Reference: Neelapu 2018.

Table 5 Recommendation for the Management of Raised Intracranial Pressure (ICP)	
Stage	**Management**
Stage 1 or 2 papilledema [a] with CSF opening pressure of <20 mmHg without cerebral edema	• Acetazolamide 1,000 mg IV, followed by 250–1,000 mg IV every 12 hours (adjust dose based on renal function and acid-base balance, monitored 1–2 times daily)
Stage 3, 4, or 5 papilloedema, [a] with any sign of cerebral oedema on imaging studies, or a CSF opening pressure of ≥20 mmHg	• Use high-dose corticosteroids with methylprednisolone IV 1 g/day, as recommended for Grade 4 encephalopathy syndrome (Table 3) • Elevate head end of the subject's bed to an angle of 30 degrees • Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 28–30 mmHg, but maintained for no longer than 24 hours • Hyperosmolar therapy with either mannitol (20 g/dL solution) or hypertonic saline (3% or 23.4%, as detailed below) – Mannitol: initial dose 0.5–1 g/kg; maintenance at 0.25–1 g/kg every 6 hours while monitoring metabolic profile and serum osmolality every 6 hours, and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40 – Hypertonic saline: initial 250 mL of 3% hypertonic saline; maintenance at 50–75 mL/h while monitoring electrolytes every 4 hours, and withhold infusion if serum Na levels reach ≥155 mEq/L – For subjects with imminent herniation: initial 30 mL of 23.4% hypertonic saline; repeat after 15 minutes, if needed • If subject has ommaya reservoir, drain CSF to target opening pressure of <20 mmHg • Consider neurosurgery consultation and IV anesthetics for burst-suppression pattern on electroencephalography

Table 5 Recommendation for the Management of Raised Intracranial Pressure (ICP)	
Stage	**Management**
	• Metabolic profiling every 6 hours and daily CT scan of head, with adjustments in usage of the aforementioned medications to prevent rebound cerebral edema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension

CSF, cerebrospinal fluid; CT, computed tomography (scan); IV, intravenous.
NOTE: All medication doses indicated are for adults.
[a] Papilledema grading should be performed according to the modified Frisén scale.
Reference: Neelapu 2018.

7.5 Tumor Lysis Syndrome (TLS)

TLS is a possible risk associated with anti-tumor therapy however the risk of TLS on this protocol is exceedingly low because patients have received recent high-dose chemotherapy and tumor bulk at time of autoHCT is low. TLS symptoms include nausea, vomiting, diarrhea, muscle cramps or twitches, weakness, numbness or tingling, fatigue, decreased urination, irregular heart rate, restlessness, irritability, delirium, hallucinations, and seizures. TLS is comprised of abnormal lab changes that include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia.

Prophylaxis for and management of TLS should be done in accordance with standard institutional practice.

7.6 Myelosuppression, Immunosuppression, Bone Marrow Failure, and Infections

Therapies used for the treatment of hematologic malignancies have been reported to cause myelosuppression (neutropenia and/or thrombocytopenia), leukopenia, anemia; and in some cases, bone marrow failure. Hematologic cytopenias could be further compounded by other factors such as underlying disease, concurrent illnesses and concomitant medications.

Close monitoring of complete blood count (CBC) and for the development of infections is strongly recommended. In general, management including transfusion support and use of growth factors, should be done in accordance with standard institutional practice.

Non-engraftment

We will collect detailed data on hematologic toxicity in Component 1 and will provide FDA with safety data for discussion before proceeding with Component 2 if any Grade 4 hematologic toxicity occurs. Therefore, we will gain safety data on FT596 and expect that the risk of non-engraftment in Component 2 will be low. Non-engraftment by Day 28 will be confirmed by bone marrow biopsy (defined as <5% marrow cellularity). To mitigate the adverse outcome, all subjects in

Component 2 will undergo HLA typing and search for an allogeneic donor (related sibling, haplo-donor or unrelated donor) for potential rescue allogeneic donor hematopoietic cell transplantation.

8 Schedule of Treatment, Tests, and Procedures

If a patient is consented after the transplant procedure, initial inclusion and exclusion criteria is abstracted for the standard of care assessment prior to transplant as permitted in the patient consent form document. No research related procedures or sample collections are permitted prior to consent signing.

For scheduling purposes, the rituximab/FT596 “package” is administered with a +3 day window from the targeted FT596 administration day (Day 30 or Day 7 post-transplant). Rituximab or an FDA approved biosimilar is given 2 to 3 days (48 to 72 hours) prior to the planned FT596 infusion.

In the event of rituximab related toxicity, the FT596 infusion may delayed for up to 7 days to permit resolution of any related adverse events to Grade 1 or better.

A ± 1 Day window is permitted for visits through the End of Treatment (EOT) visit; however, whenever feasible do not shift subsequent time points off of the targeted day (based on the actual day of the FT596 infusion).

After the EOT visit, follow-up for this study will coincide with the standard of care transplant follow-up schedule through 1 year post-transplant.

In addition, targeted days may be altered as clinically appropriate.

8.1 Required Clinical Care Evaluations

	Screening prior to Transplant	Post-Transplant Confirmation of Continuing Eligibility (approximately Day 21 for Component 1)	Day of Rituximab (Rituxan or an FDA approved biosimilar, e.g. Truxima and Ruxience) Infusion (-3 day window for labs and assessment)	Day of FT596 Infusion *(Day 0^)*	*Post FT596 Infusion (using Day 0 as the day of infusion)*					Abstract from patient's EMR at each SOC visit until the 3 month post-transplant	3, 6, and 12 months from transplant at the time of SOC visit
					day 2	*day 7*	*day 14*	*day 21*	EOT visit *day 28*		
Consent	X[1]										
Screening Assessment	X										
Brief Medical Assessment				X	X	X	X	X	X		
Medical History	X	X									X
Concomitant Medications	X			X							
Assess Venous Access		X									
Physical Exam	X	X	X								X
ICANS (neurotoxicity) monitoring – refer to Section 7.4		X		X		X[7]	X[7]	X[7]	X[7]		X
Weight	X	X	X								
Height	X										
Vitals and Pulse Oximetry	X	X	X	X					X[6]		
Toxicity Assessment	X	X	X	X	X	X	X	X	X	X	X
CBC, diff, plt	X	X	X	X	X	X	X	X	X	X	X
Basic metabolic panel (BMP)[2]				X	X	X	X	X			X
Comprehensive metabolic panel (CMP) or equivalent[3] plus magnesium, phosporus	X	X	X						X	X	
eGFR	X	X									
Urine or serum pregnancy test for WOCBP[4]	X	X									
If pt develops cytokine release syndrome (CRS): CRP, ferritin and, if testing available, IL-6				If CRS is suspected obtain CRP, ferritin and IL-6 levels At diagnosis document CRP, ferritin and IL-6 levels 3 x weekly if inpt or at every outpt visit until resolution of CRS. Refer to Section 7.3.							
If pt develops neurotoxicity				Refer to Section 7.4 for FDA recommended testing[7]							

	Screening prior to Transplant	Post-Transplant Confirmation of Continuing Eligibility (approximately Day 21 for Component 1)	Day of Rituximab (Rituxan or an FDA approved biosimilar, e.g. Truxima and Ruxience) Infusion (-3 day window for labs and assessment)	Day of FT596 Infusion *(Day 0^)*	*Post FT596 Infusion (using Day 0 as the day of infusion)*					Abstract from patient's EMR at each SOC visit until the 3 month post-transplant	3, 6, and 12 months from transplant at the time of SOC visit
					day 2	*day 7*	*day 14*	*day 21*	EOT visit *day 28*		
Disease staging	X	X									Per SOC
CXR or chest CT scan	X										
PFTs[5]	X										
EKG	X										

^ *day 0* is assigned to the day of the FT596 infusion regardless of whether the infusion is given Day 30 or Day 7 post-transplant

1 Consent is obtained prior to transplant – no re-consent required
2 basic metabolic panel consists of BUN, creatinine, calcium, glucose, lytes (CO2, Cl, Na, K)
3 comprehensive metabolic panel consists of albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, creatinine, glucose, lytes (CO2, Cl, Na,, K), total bilirubin, and total protein
4 women of child bearing potential
5 pulmonary function testing required only if symptomatic or prior known impairment
6 Vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiration rate) are performed in association with the FT596 infusion at the following time points: within 15 minutes of the infusion start, at 10 (±5) minutes during infusion, and every 15 (±5) minutes for 1 hour after the end of the last administered bag of FT596.
7 If the patient develops neurological toxicity for which cerebrospinal fluid (CSF) analysis is performed, in addition to standard clinical testing, the sample should be tested for Human Herpes Virus (HHV 6&7) per Section 7.4. In addition, quantitative testing in blood for HHV6 and HHV7 in the context of neurotoxicity should be done. I
8 Long-term follow-up continues for up to 15 years per CPRC 2020LS052

8.2 Research Related Tests and Procedures

	Prior to start of pre-transplant chemo	Post-transplant/ pre-FT596	Prior to Rituximab	*day 0*^ Prior to FT596	*Post FT596 Infusion (using Day 0 as the day of infusion)*							3, 6, and 12 months from transplant at time of SOC visit
					30 (± 5) minutes post infusion end	*day 1*	*day 3*	*day 7*	*day 14*	*day 21*	End of treatment Visit *day 28*	
ferritin, CRP (to hospital lab charge to research)		X									X	
Assess for toxicity (including DLTs and SRs) per Section 10			X	X	X	X	X	X	X	X	X	X
Six 10 ml green top tubes[1]	X	X	X	X		X	X	X	X	X	X	X (30 ml)
One 10 ml of red top tube	X	X	X	X		X	X	X	X	X	X	X (10 ml)
One 10 ml green top tube[1]					X							
Initial Safety samples: 1 x 3 ml red top serum tube 1 x 10 ml green top tube – store frozen in TTL and batch ship to Fate	X	X (only if consented after HSCT)										
Safety follow-up: 1 x 3 ml red top serum tube 1 x 10 ml green top tube 1 x 6 ml yellow top tube – store frozen in TTL and batch ship to Fate												X
PRA anti-HLA antibodies one 10 ml red top		X									X	

^ *day 0* is assigned to the day of the FT596 infusion regardless of whether the infusion is given Day 30 or Day 7 post-transplant

1- At TTL: PBMCs are isolated from the heparin/green tube at predetermined time points for PCR testing by Fate

Refer to the Laboratory Manual for additional details

If a patient is consented after HSCT, the 60 ml green tops and 10 ml red tops research related samples associated with the pre-transplant time point are not collected.

All research samples go to the Masonic Cancer Center's Translational Therapy Lab (TTL) except for the baseline and Day 28 for ferritin and CRP testing, and the PRA anti-HLA antibody samples done prior to study treatment start and at Day 28, which are charged to research but run in the treatment center's clinical lab. If additional ferritin and/or CRP levels are collected as part of good medical care (i.e. development of signs of CRS) they are to be charged as standard of care.

Note: If a patient is not abiding by the required clinical care calendar (Section 8.1), the collection schedule of research related samples may be altered or deleted or discontinued on an individual patient basis, as appropriate. During follow-up no visit will be solely for research and instead be linked with a standard of care visit closest to the targeted research related time point.

It is recognized that with novel therapies as used in this study, the timing of protocol directed research samples may miss important patient specific events. For this reason, up to 3 extra samples for a total of 210 ml of blood may be collected at additional time points that are not specified above.

Samples to evaluate lymphocyte number and phenotype will be collected as detailed above for the Masonic Cancer Center Translational Therapy Lab (TTL) along with serum (red top tubes) for measure of cytokines that can reflect immune activation.

Flow cytometry analysis of a fraction of the PBMC will detect surface markers that define lymphocyte subsets (NK, NKT, B, and T cells, both CD4 and CD8), as well as intracellular markers that define regulatory T cells (Foxp3) and proliferating cells (Ki67). All remaining PBMC will be cryopreserved in 10% DMSO and stored in liquid nitrogen for future testing, if subject agreed to future storage at the time of initial consent.

Samples may be sent to laboratories outside of the University of Minnesota in cases where testing is not available internally as embedded in the patient consent form.

9 Study Agents

9.1 FT596

FT596 is an investigational product and can only be used and administered under an FDA-approved protocol. For the purposes of this study FT596 is provided by Fate Therapeutics.

FT596 will be provided as a cryopreserved bag, thawed at the site of administration and administered as an IV infusion via gravity. FT596 must be administered using a Fate approved intravenous administration set with an in-line filter (170-260 micron).

Refer to the FT596 Storage, Handling, and Administration Guidance for additional details.

Refer to Section 7 for potential toxicities.

9.2 Rituximab (Rituxan or an FDA approved biosimilar, e.g. Truxima and Ruxience)

Trade names: Rituxan®, Truxima®, and Ruxience®
Classification: Monoclonal Antibody, Antineoplastic Agent
Category: Biological Response Modifier Agent
Dosage and Administration Schedule: For the purposes of the study, rituximab and rituximab biosimilars 375 mg/m^2 IV is administered per institutional guidelines on 2-3 days prior to FT596.
Dose Forms and Strengths: refer to specific product prescribing information
Availability: Available by prescription
Warnings and Precautions:

- Tumor lysis syndrome – administer prophylaxis and monitor renal function
- PML - monitor neurologic function. Discontinue rituximab
- Hepatitis B reactivation with fulminant hepatitis, sometimes fatal – screen high risk patients and monitor HBV carriers during and several months after therapy. Discontinue rituximab if reactivation occurs.
- Cardiac arrhythmias and angina can occur and can be life threatening. Monitor patients with these conditions closely.
- Bowel obstruction and perforation - evaluate complaints of abdominal pain.
- Do not administer live virus vaccines prior to or during rituximab.
- Monitor CBC at regular intervals for severe cytopenias
- Pregnancy Category C

Expected Toxicities:

Rituximab (Rituxan and FDA approved biosimilars)		
common	**less common**	**rare, but may be serious**
• mild allergic reaction with first infusion (may include fever, headache, chills, itching, hives, nausea, shortness of breath)	• allergic reaction with second and later infusions (same symptoms as under common) • low white blood cell count with increased risk of infection • cough • rash, itching • nausea • vomiting • diarrhea • muscle aches • runny nose • sinus infection	• serious allergic reaction, with hives, trouble breathing, tightness in the chest or throat, heart attack, or shock • serious skin reaction • kidney damage • low platelet count with increased risk of bleeding • blockage or hole in the bowel, with abdominal (belly) pain • low red blood cell count (anemia) with tiredness and weakness • death due to allergic reaction, infection, lung damage, tumor lysis syndrome, serious skin rash, bowel obstruction, liver failure from reactivated hepatitis b, and other causes

Refer to individual product prescribing information for additional information:

- Rituxan® https://www.gene.com/download/pdf/rituxan_prescribing.pdf
- Truxima® https://www.truxima.com/globalassets/truxima-dtc/pdfs/truxima-prescribing-information.pdf
- Ruxience™ http://labeling.pfizer.com/ShowLabeling.aspx?id=12090

10 Adverse Event Monitoring, Documentation, and Reporting

For the purposes of the study the FT596 in combination with rituximab (Rituxan and FDA approved biosimilars) is considered the investigational product.

For the reminder of the section rituximab is a blanket term for Rituxan and any FDA approved biosimilars.

Toxicity and adverse events will be classified and graded according to NCI's Common Terminology Criteria for Adverse Events V 5.0 (CTCAE) and reported on the schedule below. A copy of the CTCAE can be downloaded from the CTEP home page. (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)

An exception to the use of CTCAE will be for the assessment of cytokine release syndrome (CRS). Individual adverse events which are associated with CRS will be graded per CTCAE; however the ultimate assessment will be made using a revised grading system for CRS as presented by Lee et al (Lee 2019).

ASTCT Cytokine Release Syndrome Consensus Grading System [a]				
CRS Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Fever [b]	Temperature ≥38˚C	Temperature ≥38˚C	Temperature ≥38˚C	Temperature ≥38˚C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring vasopressors with/with-out vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or [c]				
Hypoxia	None	Requiring low-flow nasal cannula [d] or blow-by	Requiring high-flow nasal cannula, facemask, non-rebreather mask, or venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Organ toxicities associated with CRS may be graded according to NCI CTCAE v5.0, but they do not influence CRS grading.

[b] Fever is defined as temperature ≥38°C not attributable to any other cause. In subjects who have CRS then receive antipyretics or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[c] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring one vasopressor and hypoxia requiring low flow nasal cannula is classified as having Grade 3 CRS.

[d] Low-flow nasal cannula is defined as oxygen delivered at >6 liters/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 liters/minute.

Source: Lee et al. 2019.

The following definitions of adverse events (AEs) and serious adverse events (SAEs) will determine whether the event requires expedited reporting via the OnCore SAE Report Form in addition to routine documentation in the OnCore AE case report form (CRF).

10.1 Adverse Event Terminology

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Serious Adverse Event: An adverse event is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected Event: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

The categories for AE attribution to study treatment are as follows:

- Definite – clearly related
- Probable – likely related
- Possible – may be related
- Unlikely – doubtfully related
- Unrelated – clearly not related

The following definitions are from the Masonic Cancer Center's Standard Operating Procedure (SOP) Deviation Reporting:

Major Deviation: A deviation or violation that impacts the risks and benefits of the research; may impact subject safety, affect the integrity of research data and/or affect a subject's willingness to participate in the research. Deviations that place a subject at risk, but do not result in harm are considered to be major deviations.

Minor Deviation: A deviation or violation that does not impact subject safety, compromise the integrity of research data and/or affect a subject's willingness to participate in the research.

10.2 AE Documentation Requirements

Adverse event collection for the purposes of this study will focus on events felt to be related to FT596 and rituximab or events that cannot be attributed to other causes (i.e. transplant-related, co-morbidities).

Monitoring for adverse events will begin with the first dose of rituximab through the End of Treatment visit after FT596.

Adverse event documentation for the purposes of this study will focus on

- expected toxicities felt to be related to rituximab
- expected toxicities felt to be related to the FT596
- unexpected adverse events that cannot be attributed to the transplant procedure or other causes (i.e. underlying disease, co-morbidities)

For the purposes of this study, adverse event documentation requirements in OnCore will be based on grade, expectedness and relationship to the investigational product (FT596 and rituximab):

	Grade 1	Grade 2		Grade 3		Grade 4 and 5
	Expected or Unexpected	**Expected**	**Unexpected**	**Expected**	**Unexpected**	**Expected or Unexpected**
Unrelated Unlikely	Not required	Required	Required	Required	Required	Required
Possible Probable Definite	Not required	Required	Required	Required	Required	Required

After the End of Treatment visit, monitoring for adverse events will become less frequent based on the schedule in Section 8.1 and only events that are unexpected and at least possibly related to FT596 will be documented upon knowledge.

10.3 SAE Documentation and Reporting

Any event meeting the definition of an SAE must be documented using the paper MCC SAE Report Form.

Any event meeting the definition of serious must be reported to Masonic Cancer Center Multisite Program Manager within 24 hours of knowledge. Refer to Section 10.6.

10.4 Dose Limiting Toxicity and Excessive Toxicity (Stopping Rule Events) Documentation and Reporting Requirements

All patients enrolled in Components 1 and 2 are monitored for dose limiting toxicity (DLT) and excessive toxicity (early stopping events) specific to the Component. Refer to Section 12 for definitions. (ONLY POST FT596 EVENTS COUNT)

In addition to documenting the event in the study's CRF's, all DLT and SR events are to be documented on the Event Form found in OnCore per Masonic Cancer Center procedures.

An event that counts as a DLT does not necessarily constitute a SAE and should be reported as such only if they meet the criteria for reporting as defined in Section 10.5.

10.5 Documentation of Death and Reporting Requirements

Deaths during the treatment and follow-up period, including due to disease, will be recorded as an SAE and reported per Section 10.6. Deaths due to disease should be recorded as a Grade 5 Neoplasm.

In addition, the death date and cause must be documented in the patient follow-up tab in OnCore upon knowledge using the comment field in the survival status section to record the cause.

10.6 Institutional Event Reporting Table

Event Type	Reporting Timeframe	Form to Use	Report to
Any event meeting the definition of serious and all patient deaths	Within 24 hours of knowledge	Paper SAE Report Form	For Participating Sites: Masonic Cancer Center (MCC) Multisite Program Manager affilates@umn.edu Local institutional IRB or other entities per institutional policies and guidelines
Dose Limiting Toxicities	Within 24 hours of knowledge	DLT Event Form in OnCore	
Stopping Rule Events (Excessive Toxicity)	Within 24 hours of knowledge	Stopping Rule Event Form in OnCore	
Major Deviations, as defined in Section 10.1.	Within 5 working days of knowledge	Deviation Report Form in OnCore	
Minor Deviations, as defined in Section 10.1.	Per Institutional Policy	n/a (record in Deviations Tab)	For UMN MCC: Report to the study's regulatory specialist For Participating Sites: minor deviations are not reportable to the MCC Multisite Manager. Report to local institutional IRB or other entities per institutional policies and guidelines.

*events occurring at the University of Minnesota are reported to the study's Regulatory Specialist who will submit to other entities as usual

Individual institutional sites are responsible for reporting any event meeting local reporting requirements to their institutional IRB and/or other research oversight committees.

10.7 Expedited MCC Reporting Requirements (MCC)

As the study sponsor, the Masonic Cancer Center has the following expedited reporting responsibilities for select events reported in Section 10.6:

Agency reporting to	Criteria for reporting	Timeframe	Form to Use	Submission address/email address
Advarra (IRB of Record)	unanticipated problems involving risks to subjects or others; unanticipated adverse device effects; protocol violations that may affect the subjects' rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data; subject death; suspension of enrollment; or termination of the study	promptly and no later than 2 weeks (10 business days) from the time the investigator learns of the event	Refer to the Advarra IRB Handbook	Advarra via study specific CIRBI Link
UMN IRB	Refer to Submitting Updates in ETHOS – External IRB Study/Site			
FDA	Unexpected and fatal or unexpected and life threatening suspected adverse reaction	no later than 7 Calendar Days	MCC SAE Report Form	Submit to FDA as an amendment to IND with a copy to each participating site and Fate Therapeutics
	1) Serious and unexpected suspected adverse reaction or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure or 3) findings from other sources (other studies, animal or in vitro testing)	no later than 15 Calendar-Days		
	1) All other events per CFR 312.33 2)An annual manufacturing update, including for each new lot of the investigational biologic used in clinical trials, the lot number, the results of all tests performed on the lot, and the specifications when established (i.e., the range of acceptable results) (21 CFR 312.23(a)(7))	At time of IND annual report	Summary format	Submit as part of the IND annual report
U of MN Institutional Biosafety Committee	Any significant research-related accidents and illnesses involving potentially hazardous biological agents subject to IBC purview	As soon as possible (within 24 hours is ideal)	IBC Incident Report	Via eProtocol

11 Study Data Collection and Monitoring

11.1 Data Management

This study will collect regulatory and clinical data using University of Minnesota CTSI's instance of OnCore® (Online Enterprise Research Management Environment).

The OnCore database resides on dedicated secure and PHI compliant servers. All relevant AHC IS procedures related for PHI compliant servers (as required by the Center of Excellence for HIPAA Data) apply to OnCore databases. The informatics team grants the IRB approved study team members access to data.

Additional immune monitoring data about correlative laboratory samples generated by the Masonic Cancer Center Translational Therapy Laboratory (TTL) from the protocol-directed correlative research samples is stored in their Laboratory Information Management System (LIMS). The LIMS database application is also stored on a production server located in the UMN datacenter (WBOB) and is managed by the Academic Health Center

Key study personnel are trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore.

11.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRFs) developed within OnCore based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into OnCore at time of study entry, completing e-CRFs based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

11.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which may be accessed at http://z.umn.edu/dmsp.

For the purposes of data and safety monitoring, this study is classified as high risk (under a locally held IND). Therefore, the following requirements will be fulfilled at the University of Minnesota and at participating sites:

- At least quarterly review of the study's progress by the Masonic Cancer Center Data and Safety Monitoring Council (DSMC).
- The University of Minnesota (lead site) Principal Investigator will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The local site PIs will comply with at least twice yearly monitoring of the project by each site's internal monitoring staff.
- The University of Minnesota (lead site) Principal Investigator will oversee the submission of all reportable adverse events per Section 10.7 to the Masonic Cancer Center's SAE Coordinator, the University of Minnesota IRB; and oversee the submission of all reportable adverse events to the FDA
- The University of Minnesota (Sponsor) and the MCC CTO have oversight responsibility for trial monitoring at affiliate sites.

IND Annual Reports

In accordance with regulation 21 CFR § 312.33, the IND sponsor (Dr. Bachanova) will submit a progress report annually. The report is submitted within 60 days of the anniversary date that the IND went into effect. A copy of the report will be provided to Fate Therapeutics. Additional annual reporting requirements are found in the FDA Acknowledgment of Receipt of IND dated March 25, 2020.

11.4 Participating Site Monitoring

The PI (Dr. Bachanova) with the CTO has oversight responsibility for trial monitoring at participating sites.

Participating sites must self-monitor using the Masonic Cancer Center Data and Safety Monitoring Plan (https://www.cancer.umn.edu/for-researchers/clinical-investigator-resources/mcc-dsmp). Alternately, participating sites that are an NCI designated Cancer Center may self-monitoring using their NCI approved Data and Safety Monitoring Plan.

The investigator will permit study-related monitoring, audits, and inspections by the study's Principal Investigator/IND sponsor and/or any designees, the local IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

11.5 Teleconferences – Lead Site and Participating Sites

Regular teleconferences will be held to facilitate communication between participating sites regarding the study's progress, patient updates, summary of safety reports, case report form completion, and other issues for discussion. The University of Minnesota Participating Sites Manager is responsible for arranging these teleconferences and preparing the agenda. Meetings will occur every 2 weeks; however, these may be scheduled more or less frequently at the discretion of the lead institution. Participation of a minimum of one representative from each affiliate site is expected. These teleconferences are in addition to other previously described site interactions including centralized patient registration, institutional and MCC required reporting of safety related issues, case report form completion in the study's central database (OnCore) and affiliate oversight through self-monitoring in compliance with the Masonic Cancer Center's Data and Safety Monitoring plan.

11.6 Record Retention

The investigator will retain study records including source data, copies of case report forms, consent forms, HIPAA authorizations, and all study correspondence in a secured facility until permission is received that the documents are no longer needed.

Please contact the CTO before destroying any study related records.

12 Statistical Considerations

12.1 Study Designs

This study consists of two components. The 1st component is a Phase I clinical trial to identify the maximum tolerated dose (MTD) of FT596 at Day 30 post FT596 infusion. The second component is a Phase I clinical trial to identify the MTD of FT596 at Day 7 post FT596 infusion. Rituximab is given 2-3 days before FT596. In addition to identifying the MTD and providing preliminary estimates of safety, secondary objectives include providing preliminary descriptive estimates of efficacy such as progression-free survival, relapse and non-relapse mortality along with their error measurements. Correlative objectives include measurement of the persistence of FT596 in blood after each FT596 infusion by immunophenotyping and PCR up to 1 year, the association of FT596 persistence with safety and anti-tumor activity.

Component 1 will identify the MTD of FT596 when given as a single dose at Day 30. Up to three FT596 dose levels are planned (Dose Level 1: $9x10^7$ cells/dose, Dose Level 2: $3x10^8$ cells/dose, Dose Level 3: $9x10^8$ cells/dose with a Dose Level - 1: $3x10^7$ cells/dose tested only if DLT at DL1).

Component 1 dose limiting toxicity is defined as any of the following events within 28 days after the FT596 dosing based on CTCAE v5:

- Grade 4 hematologic toxicity lasting > 7 days (not including lymphopenia)
- Grade 4 non-hematologic toxicity
- Grade ≥3 FT596 Infusion Related Reaction
- Grade 2 acute GVHD that requires steroid therapy >7 days or progression after 3 days of steroids or has partial response after 14 days of treatment
- Grade ≥3 acute GVHD
- Grade 4 cytokine release syndrome (CRS)
- Grade 3 CRS that does not resolve to < Grade 2 in 72 hours
- Grade 3 neurotoxicity

- Grade 3 organ toxicity involving vital organs; cardiac, central nervous system and pulmonary that lasts for longer than 7 days including Grade 3 Investigations (laboratory values) of any duration that indicate damage to vital organs.
- Any Grade 3 non-hematological toxicity that does not resolve to ≤Grade 2 within 72 hours; excepting Grade 3 renal and hepatic toxicity which may take up to 7 days to resolve to ≤Grade 2

The MTD will be determined by using a modified Continual Reassessment Method (CRM). (Goodman 1995) The CRM uses a power model for the probability of DLT at each dose, where the probability of toxicity at dose i is modeled as piexp(α) where pi is a constant and α is distributed a priori as a normal random variable with mean 0 and variance 2. The goal of this CRM will be to identify one of the 3 dose levels corresponding to the desired maximum acceptable toxicity rate of ≤25%.

Initial estimates of toxicity or the "skeleton" estimates are provided by the clinician. The initial estimates or prior probability of toxicity are listed as 1%, 3%, and 6% for doses 1, 2 and 3, respectively. As the study progresses, the CRM will continually update the estimates of the toxicity probabilities.

Patients are enrolled in cohorts of 3 starting at Dose Level 1. A minimum of 28 days will separate each cohort. For Dose Level 1 a minimum of 28 days will separate each patient to assess for dose limiting toxicity (DLT). In subsequent cohorts, the 1st and 2nd patient will be separated by at least 28 days and at least 14 days will separate the 2nd and 3rd patient. Enrollment will continue in cohorts of 3 and each new cohort of 3 will be sequentially assigned to the most appropriate dose based on the updated toxicity probabilities after the 3rd patient from the previous cohort has reached 28 days. The MTD will be identified when the total sample size of 18 is exhausted or 6 patients are sequentially enrolled at the same dose. A maximum of 18 patients is used in part due to low expected toxicity. The function 'crm' from the R package 'dfcrm' will calculate posterior means of toxicity probabilities. The CRM uses a Bayesian framework that combines experience from patients in the earlier part of the trial with the clinician's initial best estimate of the toxicity rates at each dose level to estimate a dose level that best corresponds to the target toxicity of ≤25%. Dose escalation of more than one level is not permitted with this design.

Component 2 will use a similar design but identify the MTD of FT596 when given as a single dose at Day 7. Up to two dose levels of FT596 are planned (1 Dose Level below the MTD from component 1 and the MTD from component 1) so any two sequential dose levels of the following may be included (Dose Level -1: 3x10^7

cells/dose, Dose Level 1: $9x10^7$ cells/dose, Dose Level 2: $3x10^8$ cells/dose, Dose Level 3: $9x10^8$ cells/dose).

The DLT events for Component 2 are the same as in Component 1 except for the addition of:

- Non-engraftment by Day 28 post-transplant

The MTD will be identified in the same fashion as Component 1 except that the initial estimates or prior probability of toxicity may be slightly higher due to the infusion of cells at Day 7 plus the additional possible DLT event. Assuming that we start at Dose Level 2, the skeleton probabilities might be listed as 5% and 10% for doses 2 and 3, respectively. The target toxicity level will still be ≤25%. As in Component 1, the CRM will continually update the estimates of the toxicity probabilities of both doses; first at the end of 28 days post infusion for each of the first three patients; and at the end of the of 28 day follow-up for the last patient in each of the 3 patient cohorts beyond the initial 3 patients. A minimum of 28 days will separate each patient in the 1st cohort to assess for dose limiting toxicity (DLT). In subsequent cohorts, the 1st and 2nd patient will be separated by at least 28 days and at least 14 days will separate the 2nd and 3rd patient.

As in Component 1, each new cohort of three patients will be sequentially assigned to the most appropriate dose based on the updated toxicity probabilities, and the MTD will be identified when a total sample size of 18 is exhausted or 6 patients are sequentially enrolled at the same dose.

12.2 Sample Size

Due to the low expected toxicity, a maximum of 18 patients will be enrolled during component 1. Based on the simulations from table 1, this should be sufficient and safe to define the MTD for component 1. Based on the simulations from table 2, component 2 should also be sufficient and safe to define the MTD. Enrollment will most likely include 12 patients under each component but could range from 2 to 18 patients. With expected enrollment of 12-18 patients/year, accrual for each component should be complete within 1.5 years. So after combining both trials, accrual should be complete in 2.5-3 years.

Table 1. **Operating characteristics for CRM (component 1)**

Cells/ dose	Expected DLT			Excessive DLT		
	True Probability	Probability of dose	Patient Number	True Probability	Probability of selecting dose	Patient Number
$9x10^7$	1%	0%	3	10%	15%	6
$3x10^8$	3%	0%	3	25%	51%	6
$9x10^8$	6%	100%	6	40%	34%	6

Table 2. Operating characteristics for CRM (likely scenario: component 2)

Cells/ dose	Expected DLT			Excessive DLT		
	True Probability	Probability of dose	Patient Number	True Probability	Probability of selecting dose	Patient Number
$3x10^8$	5%	0%	6	25%	74%	6
$9x10^8$	10%	100%	6	40%	26%	6

12.3 Statistical Analysis

The MTD will be determined in Component 1 and Component 2 per the design. All other endpoints including safety, progression-free survival, relapse, non-relapse mortality, toxicity rates and other clinical activity will be estimated descriptively. This will include simple frequencies, proportions, means, standard deviations/standard errors, medians and ranges.

12.4 Monitoring Guidelines

Monitoring guidelines will be in place to monitor events separately for each component separately. Stopping guidelines will be enacted using a continuous monitoring strategy based on an adaptation of Pocock stopping boundaries. (Ivanova 2005) In the event that the stopping rule is triggered, enrollment will be halted. The event will be reviewed by the study team with follow-up reporting of the findings to the FDA and IRB before enrollment is restarted.

The rules are based on the time from transplant and occurring after the FT596 infusion.

12.4.1 Mortality by Day 100

Enrollment will be halted and reviewed by the study team with follow-up notification to the FDA and IRB of the findings before enrollment is restarted.

12.4.2 Grade III-IV Acute GVHD by Day 100

Enrollment will be halted and reviewed by the study team with follow-up notification to the FDA and IRB of the findings before enrollment is restarted.

12.4.3 Any Grade 4 FT596 Infusion Related Reaction

Enrollment will be halted and reviewed by the study team with follow-up notification to the FDA and IRB of the findings before enrollment is restarted.

12.4.4 Any Two Grade 4 Dose Limiting Toxicities (DLTs)

If two Grade 4 DLTs occur, enrollment will be halted and reviewed by the study team with follow-up notification to the FDA and IRB of the findings before enrollment is restarted.

12.4.5 Grade 4 Lymphopenia (<200 cells/uL) at Day 100

The goal is to construct a boundary based on lymphopenia such that the probability of early stopping is at most 10% if the rate is equal to 20% and our sample size is at most 18. With these stipulations, the trial will be stopped and reviewed if 3/4, 4/7, 5/10, 6/13 or 7/17 patients at any time have Grade 4 related lymphopenia at Day 100.

12.4.6 Engraftment Failure by Day 28 (Component 2 only)

Enrollment will be halted to Component 2 and reviewed by the study team with follow-up notification to the FDA and IRB of the findings before enrollment is restarted.

13 Conduct of the Study

13.1 Good Clinical Practice

The study will be conducted in accordance the appropriate regulatory requirement(s). Essential clinical documents are maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

13.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, consent, written information given to the patients, safety updates, progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

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Appendix I – LUGANO 2014 CLASSIFICATION: TUMOR RESPONSE ASSESSMENT IN LYMPHOMA

Method of Assessment

Assessments regarding sites of disease in subjects with lymphoma based on clinical, laboratory and radiographic evaluation are summarized in Table A. Positron emission tomography (PET)-computed tomography (CT) scan is the recommended radiographic modality for fluorodeoxyglucose (FDG)-avid, nodal lymphomas. For lymphomas that are not FDG-avid, anatomic CT scans should be used.

Bone marrow assessments will be based on morphologic evaluation of bone marrow biopsies. Immunohistochemistry may be used to assess response if the sample is indeterminate by morphology. Bone marrow biopsies are not required if there is positive FDG-PET uptake in the bone marrow. Otherwise, in this study of subjects with relapsed/refractory lymphoma a bone marrow biopsy should be performed only under the following circumstances:

- A bone marrow biopsy is required at baseline if the subject had a history of bone marrow involvement with lymphoma prior to the start of study treatment;
- During the course of the study, if new abnormalities in the peripheral blood counts or blood smear cause clinical suspicion of bone marrow involvement with lymphoma;
- During the course of the study, a bone marrow biopsy must be performed to confirm a radiographic CR and show no morphologic evidence of disease, or be negative by immunohistochemistry if indeterminate morphology, to assign an overall response of CR.

Table A - Lugano 2014 Classification: Criteria for Site Involvement

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

CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.

[a] PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

Reference: Cheson 2014.

1 TIMING OF ASSESSMENTS

This is a post-transplant protocol. Assessments will be per institutional standard of care.

2 IDENTIFICATION AND FOLLOW-UP OF TUMOR LESIONS BY PET-CT SCAN

Identification and follow-up of tumor lesions by PET-CT scans are based on focal uptake in nodal and extranodal sites that are consistent with lymphoma based on distribution and/or characteristics as visualized by anatomic CT scan. Unlike tumor assessments based exclusively on anatomic CT scan, no distinction between target and non-target lesions based on PET scans is required.

3 IDENTIFICATION AND FOLLOW-UP OF TUMOR LESIONS BY ANATOMIC CT SCAN

3.1 Target and Non-target Lesions

Identification and follow-up of target lesions using anatomic CT scans should include up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters should be identified from different body regions representative of the subject's overall disease burden. Where applicable, these should include mediastinal and retroperitoneal disease. Definitions of baseline measurable disease are as follows, lesions not fulfilling these definitions are designated non-measurable:

- *Nodal lesion:* must be greater than 15 mm in the longest diameter (LDi)
- *Extranodal lesion:* should be greater than 10 mm in the LDi

Measurable extranodal disease may be included among the six representative measured lesions. Overall target lesion burden is expressed as the sum of the product of the perpendicular diameters (SPD).

All other lesions including non-measurable disease and measurable disease beyond the six designated target lesions should be followed as non-measured disease as non-target lesions, e.g., cutaneous, GI, spleen, liver, kidneys, pleural or pericardial effusions, ascites, bone, and bone marrow.

3.2 Split Lesions and Confluent Lesions

Lesions may split or may become confluent over time. In the case of split lesions from a designated target lesion, the individual products of the perpendicular diameters (PPD) for each split lesion should be summed together to represent the PPD derived from the initial target lesion; this PPD is added to the sum of the PPDs of the remaining lesions to determine target lesion SPD. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression.

In the case of confluent lesions from designated target lesions, the PPD of the confluent mass should be compared with the SPDs of the individual lesions. A >50% increase in PPD of the confluent lesion compared with the SPD of individual lesions would therefore constitute progressive disease.

3.3 Definitions of Tumor Response and Progression

Target lesion responses will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

For non-target lesions in the absence of quantitative measurement, responses will be characterized as follows: CR, Non-CR/Non-PD (corresponding to PR/MR/SD), or PD.

For both target and non-target lesions, a response category of not evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status.

The best overall response (BOR) will be determined based on an overall evaluation of target lesions, non-target lesions and new lesions as summarized in Table B. The BOR is defined as the best overall response recorded from the start of study treatment until disease progression or relapse. The baseline measurement will be taken as a reference for determinations of response. The nadir measurement will be taken as a reference for PD; this measurement constitutes the smallest measurement recorded, including the baseline measurement if this is the smallest measurement.

Confirmation of overall response is not required. Confirmation of PD may be warranted, e.g., small FDG-PET avid lesions that do not fulfill the dimensional criteria for PD but are confirmed to be progressive disease based on histologic examination or continued growth of the lesion.

Table B Lugano 2014 Classification: Response Categories			
Response	**Site**	**PET-CT–Based Response**	**CT-Based Response**
Complete Response		Complete metabolic response	Complete radiologic response (all of the following)
	Lymph nodes and extralymphatic sites	Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b]	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
	Non-measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response		Partial metabolic response	Partial remission (all of the following)
	Lymph nodes and extralymphatic sites	Score 4 or 5 [b] with reduced uptake compared with baseline and residual mass(es) of any size	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
		At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
		At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
			For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Non-measured lesions	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
Stable Disease		No metabolic response	Stable disease
	Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Non-measured lesions	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable

Table B Lugano 2014 Classification: Response Categories			
Response	**Site**	**PET-CT–Based Response**	**CT-Based Response**
Progressive Disease		Progressive metabolic disease	Progressive disease (requires at least 1 of the following)
	Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
	Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≤50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions ≤2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
	Non-measured lesions	None	New or clear progression of preexisting non-measured lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

[a] A score of 3 in many subjects indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but

Table B Lugano 2014 Classification: Response Categories			
Response	**Site**	**PET-CT–Based Response**	**CT-Based Response**
should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors). [b] PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma. Reference: Cheson 2014.			