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

Study of FT538 in Combination with Daratumumab in Acute Myeloid Leukemia

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Principal Investigator/IND Sponsor:
Joseph Maakaron, MD
Division of Hematology/Oncology/Transplantation
Medicine Hematology Office
420 Delaware Street SE MMC 480
Minneapolis, MN 55455
Phone: 612-625-8942 (Administrative phone)
Email: maaka001@umn.edu

Collaborators:
Daniel Weisdorf, MD
Margaret L. Macmillan, MD (pediatrics)
Jeffrey S. Miller, MD*
David H. McKenna, Jr., MD*
*Will not consent patients to enroll on study

Biostatistician:
Ryan Shanley, MS
University of Minnesota

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Revision History

Revision #	Version Date	Revision Details	Consent Revision
	Oct 28, 2020	Original to FDA	n/a
	Dec 7 2020	Original to CPRC Synopsis, Section 3, Section 4, and Section 7: In response to the clinical IR dated Nov 27 2020 – Delay pediatric enrollment until a minimum of 6 adults are treated on this study and/or the combination arm on Fate's FT538-101 and safety data is submitted to the FDA for their review and permission to proceed with the enrollment of children is received. Minor edits and clarifications in Section 8 and Section 10.	n/a
	Jan 27 2021	In response to CPRC stipulations – updates to Section 12 and other relevant protocol sections (increasing expected enrollment to 17 from 15 patients). Updates from CCPM: • Schema: delete Day +24 under description of DARA administration plan as artifact previously missed. • Synopsis, Schema, Section 3, Section 5: Correct intra cohort enrollment plan from no staggering required to "A minimum of 14 days must pass between the enrollment of the 1st and the 2nd patient in 3 patient cohorts." to match language in Section 12. • Synopsis, Section 4.1: prior allogenic HSCT permitted but remove reference to relapse • Synopsis, Section 4.3.13: remove relapse contingency for exclusion for allogeneic HSCT within previous 90 days Other general updates: • update protocol that DARA will be purchased for the study, • delete reference of Monday as 1st day of FT538 through-out while retaining Monday as Day 1 on an example calendar in Section 6. • update LTFU study number to CPRC 2020LS220, remove the "0" from the MT number to read MT2020-33 • update Section 3 study design for clarity, correct Section numbers for DLT and SRs • other minor edits/updates throughout	n/a
1	Mar 11 2022	• Section 6 introduction and Section 6.4 - permit the use of hydroxyurea during study treatment as needed for the control of peripheral blood blasts and/or white blood count. • Update title page to reflect Dr. Maakaron also is the IND sponsor and change in statistician, delete Key Study Staff Contact Information on page 2 as no longer needed. • Section 11.3 – list Dr. Maakaron as the IND S/I, add Dr. MacMillan as pediatric physician. Minor changes/edits identified during and since the study initiation visit (SIV) in Aug 2021: • Update abbreviation table with SUSAR and S/I	simplify FT538 enrollment plan and clean-up

Revision #	Version Date	Revision Details	Consent Revision
		• Schema, Section 3 -Simplify how enrollment plan is written without change to content. • Synopsis, Section 4.2.3 – update KPS/Lansky lower eligibility limit from ≥80 to ≥70 (from SIV) • Synopsis, Section 4.2.4 – clarify lab work is done within 14 days **prior** to start of study treatment, delete cardiac requirement as addressed in exclusion criteria Section 4.3.4. • Section 6.1 – clarify monitoring section for daratumumab • Section 6.5 - expand duration of treatment section to include end of treatment assessment with reminder stopping rules monitoring is through Day 42. • Section 6.6 - clarify follow-up for disease response/survival • Section 8 – clarify the timing of the end of DLT/EOT assessment as both are scheduled for Day 29 • Section 8.1 – eliminate ICANS assessment at screening and Day -5 as neuro changes are associated with FT538 • Section 8.2 – add yellow top tube baseline safety samples for Fate in the event a patient had previously received a Fate product that used a lentivirus vector in manufacturing • Section 10.1 – remove the definition of protocol deviation as defined only applicable to studies covered by UMN IRB • Section 10.2 – clarify any event meeting the definition of serious must be recorded as an AE, clarify the reporting of abnormal lab values and assessments • Appendix III – CY/FLU adverse events – replace section wording to match Fate Therapeutics' sponsored trials • Through-out the protocol delete the CPRC number for the LTFU protocol as being replaced by a master LTFU protocol • Other minor edits/clarifications	
	Nov 24 2022	Rationale for current amendment: please see section 2.5, bottom of page 18. • Synopsis, schema, section 2.5, section 6.2- Update to lymphodepletion fludarabine days given (-6 to -2) and cyclophosphamide dosing (changed from 300mg/m^2 to 60 mg/kg), spacing between subjects in final cohort • Section 3 – updates to fast-track cohort spacing between subjects in expansion • Section 6 – updated table in treatment plan to reflect updated LD • Section 6.3.1 – minor clarification to DLT events • Section 7 - minor clarification to ensure proper classification of febrile neutropenia events per protocol • Section 8.1 – updated clinical Schedule of Treatments to reflect day -6 and day -2 • Section 8.2 – updated Research Related Tests and Procedures to include bone marrow biopsy at day +3 (±1 day) • Section 12.1-updated fast-track cohort spacing in statistics section to reflect changes in section 3	

Revision #	Version Date	Revision Details	Consent Revision
	03/23/2023	Synopsis, schema, section 6.1 – revised to reflect that daratumumab reduced to one dose from four Section 2.5 – revised to address reduction in daratumumab Section 4.2.5 – revised to update contraceptive use guidelines Section 8.1 and 8.2 – revised to remove days 10 and 17 to reflect updated treatment schedule/adjust research blood draws accordingly Appendix VI: added to document previous study schema Minor corrections of typos/formatting throughout Consent: revised to include language re: risk of xenotransplantation required by FDA	Y
	04/20/2023	Section 12.1: fixed typo in paragraph 3, dose level 3 is $1x10^9$ cells Appendix V and VI: per CPRC recommendation updated titles with more information re: previous versions	n
	05/08/2023	Corrected typo in section 12.1 per CPRC request.	n

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Key Abbreviations

Abbreviation	Definition
ABW	actual body weight
ADL	activities of daily living
AE	adverse event
AML	acute myelogenous leukemia
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete remission
CRi	complete remission with incomplete count recovery
CRM	continuous reassessment method
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
ELN	The European LeukemiaNet
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
ICANS	immune cell associated neurotoxicity syndrome
ICH	International Conference on Harmonization
rHuPH20	recombinant human hyaluronidase PH20
IL-15RF	IL-15 receptor alpha fusion protein
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
LTFU	long-term follow-up
MLFS	Morphological Leukemia Free State
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	progression free survival
PFT	pulmonary function test
RECISTv5	Response Evaluation Criteria in Solid Tumors version 5
rhIL-15	Recombinant human interleukin-15
SAE	serious adverse event
S/I	Sponsor/Investigator
SOC	standard of care
SR	stopping rule
subQ	subcutaneous
SUSAR	Suspected Unexpected Serious Adverse Reaction
TRM	treatment related mortality
ULN	upper limit of normal

Protocol Synopsis

Study of FT538 in Combination with Daratumumab in Acute Myeloid Leukemia
CPRC #2020LS114 / MT2020-33

Study Design:	This Phase I open-label dose escalation study is conducted in two stages with a primary endpoint to identify the maximum tolerated dose (MTD) of FT538 when administered with daratumumab in patients 12 years of age and older with advanced acute myeloid leukemia (AML) and related myeloid diseases. FT538 is an off-the-shelf product comprised of allogeneic natural killer (NK) cell immunotherapy lacking CD38 and expressing hnCD16 and IL-15RF. Daratumumab is a targeted therapy (IgG1k human monoclonal antibody) that targets CD38. FT538 is administered once a week for 3 consecutive weeks (Day 1, Day 8, and Day 15). Up to 5 dose levels will be tested. Fixed dose subcutaneous daratumumab is given on Day -5 prior to the NK cells as lymphodepletion. A course of outpatient lymphodepleting chemotherapy is given from Day -6 to Day -2 to promote adoptive transfer. The primary analysis for Phase I is intent-to-treat in that all patients receiving the 1st infusion of FT538 are evaluable for toxicity and efficacy. Patients who discontinue therapy prior to the first FT538 will be replaced. All patients are monitored for dose limiting toxicity and early stopping rule events as part of the event assessment. Patients are followed for 1 year from the 1st FT538 cell infusion to determine disease free survival, treatment related mortality, and time to and incidence of relapse.
Enrollment Plan:	There are five potential FT538 Dose Levels (DL). The starting dose is FT538 $1x10^8$ cells per dose with a lower safety dose of $5x10^7$ if needed (Dose Level -1). The subsequent planned FT538 cohorts are $3x10^8$, $1x10^9$, and $1.5\ x10^9$ FT538 cells per dose. The trial is conducted with no intra-patient escalation. **STAGE 1 STEP 1 Fast-track design (1 patient per dose cohort)** Start at Dose Level 1 (DL1), enroll 1 patient per dose cohort separated by 28 days (DLT period) until the: • **1st pre-defined adverse event** defined as any Grade 3 non-hematologic AE within 72 hours of a FT538 infusion • and the patient completes the 28 day DLT period with no DLT- **Activate Stage 1 Step 2** OR • **1st DLT event** within 28 days after the 1st dose of FT538 as defined in the Schema and in Section 6.3.1 - **Activate Stage 2** (Stage 1 Step 2 is not used) OR • **10 patients are treated at the Dose Level 4** (This completes enrollment - Stage 1 Step 2 and Stage 2 are not used) o If the first patient at dose level 4 in stage 1 step 1 completes DLT period with no pre-defined adverse events or DLT, successive subjects may enroll without staggering. For Dose Level 4, if no pre-defined adverse events or DLT events occur within monitoring period for the first patient, subsequent 9 subjects may enroll without staggering **STAGE 1 STEP 2 Expand current Dose Level and subsequent DLs to 3 patients** The cohort size increases from 1 to 3 patients to explore the occurrence of an AE. Two additional patients added to the current cohort without staggering. Continue dose escalation until: • **1st DLT event** as defined in the Schema and Section 6.3.1 - **Activate Stage 2** OR • **10 patients are treated at the Dose Level 4** (This completes enrollment and Stage 2 is not used.) o For Dose Level 4 in stage 1, step 2, second and third patients may enroll immediately but must complete their DLT period prior to enrolling the rest. If no DLT events within monitoring period, successive subjects may enroll without staggering **STAGE 2 Continual Reassessment Method (CRM) at the 1st DLT**

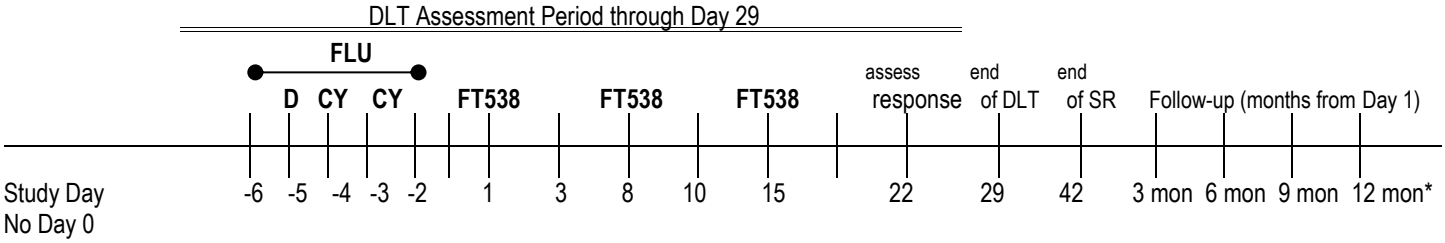
	The study design changes to the CRM. Enrollment occurs in cohorts of three. A minimum of 14 days must pass between the enrollment of the 1st and the 2nd patient in 3- patient cohorts. Each new cohort of three patients is sequentially assigned to the most appropriate dose by the study statistician based on the updated toxicity probabilities once the 3rd patient in a cohort reaches Day 29 (end of DLT period). The MTD is identified by the minimum of the following criteria: (1) the total Stage 2 maximum sample size of 25 is exhausted or (2) 10 consecutive patients are enrolled at the same FT538 dose.
Investigational Products:	Fate FT538 Daratumumab and hyaluronidase-fihj (DARZALEX FASPRO™) for subcutaneous administration
Long-Term Follow-up:	As FT538 is an engineered cellular product long-term follow-up (LTFU) is recommended by the FDA for any patient receiving at least one dose of FT538. Clinical safety information is collected at post-treatment follow-up visits or through telephone calls, medical record review, and/or e-mail/mail for up to 15 years as described in the companion LTFU protocol. Consent to LTFU is required for participation in this treatment study.
Study Rationale:	FT538 is an allogeneic natural killer (NK)-cell immunotherapy produced from a clonal master human-induced pluripotent stem cell (iPSC) line with the following engineered elements: a) deletion of the gene encoding CD38 (i.e., CD38 knockout to overcome killing of the infused FT538 product by daratumumab); b) high-affinity, non-cleavable CD16 receptor (hnCD16) to bind daratumumab; and c) interleukin (IL)-15/IL-15 receptor alpha fusion protein (IL-15RF) to enhance survival and activity of NK cells after adoptive transfer. The engineered features of FT538 are designed to result in increased activity against target tumor cells as monotherapy and when combined with monoclonal antibodies (mAbs) that can mediate antibody-dependent cellular cytotoxicity (ADCC). Daratumumab is a targeted therapy (IgG1k human monoclonal antibody) that targets CD38. While daratumumab is FDA approved for treatment of multiple myeloma, it is not approved for AML. However, a majority of AML blasts express CD38 and daratumumab can mediate antibody dependent cellular cytotoxicity by NK cells.
Primary Objective	To determine the maximum tolerated dose (MTD) of FT538 when given in combination with daratumumab in the treatment of acute myeloid leukemia.
Secondary Objectives:	• To obtain preliminary estimates of efficacy as measured by the objective response (CR + CRi) assessed by Day 28, the primary trial endpoint based on the 2017 European LeukemiaNet (ELN) response criteria (Döhner 2017) • Estimate the overall response rate (ORR) at 1 year of follow-up • Estimate disease free survival (DFS) and overall survival (OS) at 1 year of follow up • Determine safety of this combination as outlined by incidence of adverse events (AEs) based on CTCAE v5.0
Correlative Objectives:	• Change in level of expression of CD38 on leukemic blasts and normal tissue over time as determined by CD38 measurement by flow cytometry on predefined time points • Determination of the PK of FT538 in the peripheral blood and marrow • Clinicopathological correlates of efficacy (level of CD38 expression, cytogenetics and molecular classification of the disease) • Clinicopathological correlates of safety (level of CD38 expression, cytogenetics and molecular classification of the disease) • Characterization of the kinetics of changes in CD38-expressing host immune cell populations including NK, Treg and MDSCs after exposure to daratumumab
Disease Related Inclusion:	Acute myeloid leukemia relapsed/refractory after 2 lines of therapy with CD38 expression • CD38 expression is defined by ≥20% of malignant cells with CD38 expression by flow cytometry on the most recent marrow biopsy (must be within 30 days of study enrollment). • Relapsed/refractory is defined as failure to achieve at least a Morphological Leukemia Free State (MLFS) or reverting from MLF i.e. any level of blasts detected by flow cytometry. • Lines of therapy are defined as: ○ One cycle of Intensive induction chemotherapy such as 7+3, 5+2, MEC, FLAG, FLAG-Ida, or CLAG ± small molecule inhibitor

	○ Four weeks of HMA-based induction ± small molecule inhibitor ○ Hematopoietic stem cell transplantation (HSCT), must be >90 days post ○ Gemtuzumab Ozogamicin ○ LDAC + glasdegib ○ Biomarker-specific targeted agents (FLT3 inhibitors, IDH1/2 inhibitors, others if available) ○ Other treatments maybe considered after discussion with the PI
Key Inclusion Criteria:	• Age 12 years or older at the time of consent • Weight ≥ 50 kg due to FT538 fixed cell dosing and FT538 product pre-dosed packaging • Karnofsky performance status of 70-100% for age ≥16 years, Lansky play score of 70-100 for age <16 years • Evidence of adequate organ function within 14 days prior to starting study treatment defined as: ○ Estimated Glomerular Filtration Rate (estimated creatinine clearance) ≥50 mL/minute ○ Total bilirubin ≤ 5 × upper limit normal (ULN), not applicable for patients with Gilbert's syndrome • AST ≤3 × ULN and ALT ≤ 3 × ULN, not applicable if determined to be directly due to underlying malignancy Sexually active women of child-bearing potential and males with female partners of childbearing potential must agree to use must use a highly effective form of contraception as detailed in Section 4.2.5 • Must agree to and sign the consent for the companion Long-Term Follow-Up study to fulfill the FDA required 15 years of follow-up for a genetically modified cell product • Patient ≥18 years provides voluntary written consent prior to the performance of any research related procedure. Minors (<18 years) provide voluntary written assent with the parent/guardian signing the treatment consent prior to the performance of any research related procedure.
Key Exclusion Criteria:	• Diagnosis of acute promyelocytic leukemia (APL) • Pregnant or breastfeeding, Menstruating females of child-bearing potential must have a negative pregnancy test within 14 days of study treatment start • Known allergy to any of study drugs or their components • Clinically significant cardiovascular disease including any of the following: myocardial infarction within 6 months prior to first study treatment; unstable angina or congestive heart failure of New York Heart Association Grade 2 or higher or cardiac ejection fraction <40% • Any known condition that requires systemic immunosuppressive therapy (> 5mg prednisone daily or equivalent) during the FT538 dosing period (3 days before the 1st dose through 14 days after the last dose) excluding pre-medications – inhaled and topical steroids are permitted • Receipt of any biological therapy, chemotherapy, or radiation therapy, except for palliative purposes, within 2 weeks prior to Day 1 or five half-lives, whichever is shorter; or any investigational therapy within 28 days prior to the to the first dose of daratumumab. • Known active central nervous system (CNS) involvement or treated CNS disease that has not cleared. If prior disease- related CNS involvement, then must have completed effective treatment of their CNS disease • Non-malignant CNS disease such as epilepsy, CNS vasculitis, or neurodegenerative disease or receipt of medications for these conditions in the 2-year period leading up to study enrollment • Clinically significant untreated/uncontrolled infection • Live vaccine <6 weeks prior to start of lympho-conditioning • Known seropositive for HIV or known Hepatitis B or C infection with detectable viral load by PCR • Prior solid organ transplant • Allogeneic HSCT within previous 90 days • Active GVHD requiring systemic immune suppression within 14 days prior to enrollment • Presence of any medical or social issues that are likely to interfere with study conduct or may cause increased risk to the participant.
Enrollment Plan:	Enrollment for adults on this trial will not begin until all patients on the AML monotherapy Dose Cohort 1 clear the DLT window in the Fate sponsored Protocol FT538-101: FT538 as Monotherapy and in Combination with mAbs in Advanced Hematologic Malignancies.

	Enrollment of pediatric patients 12 years and older will not begin until a minimum of 6 adults are treated on this study and/or the combination arm on FT538-101 and safety data is submitted to the FDA for their review and permission to proceed with the enrollment of children is received. Enrollment will most likely include 17 patients or it could be as high as 25 patients if DLTs are encountered early. With 10-12 patients enrolled per year, accrual is expected to be completed within 1.5 to 2 years.

Study Schema (Amended 03/01/2023)[1]

There is no Day 0 in this treatment plan.



D: DARZALEX FASPRO (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously (subQ) once on Day -5

FLU: fludarabine (FLU) 25 mg/m^2 administered by IV infusion for 5 consecutive days, Day -6, Day -5, Day -4, Day -3, and day -2.

CY: Cyclophosphamide 60 mg/kg administered by IV infusion for 2 consecutive days, Day -4 and Day -3

FT538: administered at assigned dose as an IV infusion via gravity on Day 1, Day 8, and Day 15

All patients are monitored for dose limiting toxicities (DLTs) and unacceptable toxicity using early stopping rules (SRs)
Day 29 end of dose limiting toxicity (DLT) assessment (DLTs are defined on the next page and in Section 6.3.1 of the protocol)
Day 42 end monitoring for excessive toxicity (SR events are defined on the next page and in Section 6.3.2 of the protocol)

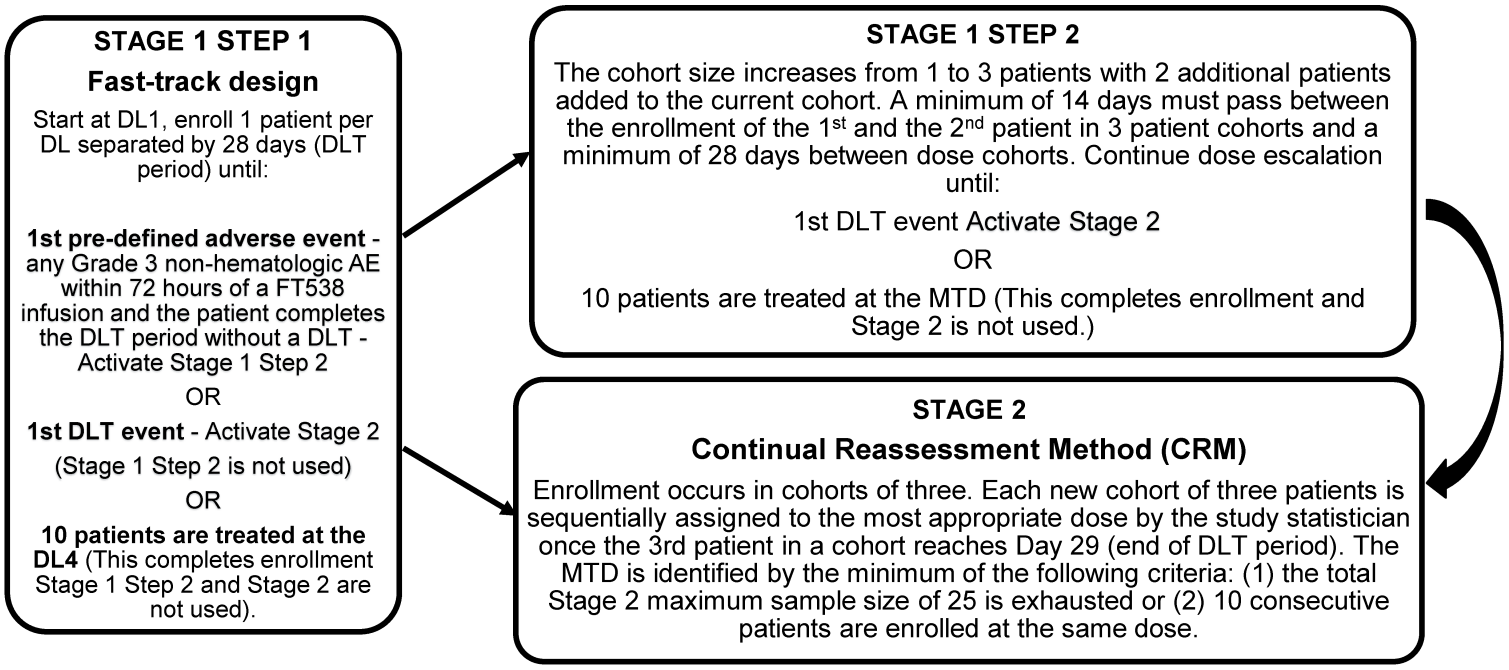
*after the 12 month visit, follow-up transfers to the long-term follow-up (LTFU) study

Up to 5 dose levels of FT538 will be tested (including, a DL -1, only used in event of DLT at DL 1):

Dose Level (DL) Cohort	FT538 cells/dose
-1	5×10^7
1 (start)	1×10^8
2	3×10^8
3	1×10^9
4	1.5×10^9

Each DL Cohort is separated by a minimum of 28 days (end of the DLT period). A minimum of 14 days must pass between the enrollment of the 1st and the 2nd patient in 3 patient cohorts.

[1] Subjects enrolled prior to 16-Nov-2022 received Cy-Flu lymphodepletion on day -4 and day -3 only; subjects enrolled prior to 20-Mar-2023 received 5 doses of daratumumab on day -12, -5, day +3 and day +17. See Appendix V for previous versions of schema.



Dose Limiting Toxicity (DLT) is defined as any AE (based on CTCAE v5) that is at least possibly related to FT538 and not related to disease progression that occurs after the first FT538 infusion through the end of the DLT assessment period on Day 29 as defined below:

Dose Limiting Toxicity (DLT)	Exceptions
• Any Grade 4 non-hematologic AE	• Fever associated with CRS that occurs in the context of Grade <3 CRS
• Grade 3 pulmonary or cardiac AE of any duration • Grade 3 immune cell associated neurotoxicity syndrome (ICANS) of any duration • Any other Grade 3 non-hematologic AE of >72 hours duration	• Grade 3 renal or hepatic AE lasting < 7 days • Grade 3 fatigue lasting ≤ 3 days • Grade 3 laboratory abnormality, unless otherwise specified that is asymptomatic and not clinically significant
• Grade ≥2 acute GvHD requiring systemic steroid administration	

All patients receiving the FT538 cell product will be monitored for unacceptable toxicity using early study stopping rules (SR) defined as:

- Excessive treatment emergent adverse events that meet DLT criteria within 15 days of the 1st FT538 - The trial will be stopped if the posterior probability that the lowest dose is unacceptably toxic (> 25% of patients) is greater than 80%;
- Grade 4 or greater FT538 infusion related reaction;
- Aplasia at Day 42 (ANC <500) after at least 1 week of growth factor (i.e. G-CSF) with an aplastic bone marrow in the absence of leukemia (<5% cellularity);
- Any death within 28 days after the last dose of FT538 and not attributable to disease progression.

If no pre-defined adverse events (grade 3 non-hematologic AE within 72 hours of product) or DLTs in any previous cohorts: after 1st subject at dose level 4 completes DLT monitoring period, patients at dose level 4 may enroll without a waiting period.

If any pre-defined adverse events BUT no DLTs in previous cohorts, after 3rd subject at dose level 4 successive subjects at dose level 4 may enroll without a waiting period.

1 Objectives

1.1 Primary Objective

The primary objective of this study is to determine the maximum tolerated dose (MTD) of FT538 when given in combination with daratumumab in the treatment of acute myeloid leukemia.

1.2 Secondary Objectives

- To obtain preliminary estimates of efficacy as measured by the objective response (CR + CRi) assessed by Day 28, the primary trial endpoint based on the 2017 European LeukemiaNet (ELN) response criteria (Döhner 2017)
- Determine the overall response rate (ORR) at 1 year of follow-up
- Determine progression free survival (PFS) and overall survival (OS) at 1 year of follow up
- Determine safety of this combination as outlined by incidence of adverse events (AEs) measured by CTCAE v5.0

1.3 Correlative Objectives

Correlative/exploratory objective include:

- Change in level of expression of CD38 on leukemic blasts and normal tissue over time as determined by CD38 measurement by flow cytometry on predefined time points
- Determination of the PK of FT538 in the peripheral blood and marrow
- Clinicopathological correlates of efficacy (level of CD38 expression, cytogenetics and molecular classification of the disease)
- Clinicopathological correlates of safety (level of CD38 expression, cytogenetics and molecular classification of the disease)
- Characterization of the kinetics of changes in CD38-expressing host immune cell populations including NK, Treg and MDSCs after exposure to daratumumab

2 Background and Significance

2.1 Introduction and Disease Under Treatment

Treatment of relapsed and refractory acute myeloid leukemia (AML) remains an unmet need given that most patients are diagnosed at an advanced age and have significant comorbidities. Strategies other than cytotoxic chemotherapy are desperately needed. CD38 is an ADP ribosyl cyclase membrane glycoprotein that is expressed in the majority of lymphocytes and on early myeloid precursors. (Drach 1994) Its presence has been has been variably reported on AML blasts. (Dos Santos 2014) We examined 51 bone marrow aspirates for presence of

absence of CD38 by clinical-grade multicolor flow cytometry and found 39/51 (76%) to have some level of expression of CD38 on AML blasts.(unpublished data) Ligation and activation of CD38 has been linked to increased superoxide generation and increase in colony forming units of cell line.(Malavasi 2008) Inhibition of CD38 with DARA has been shown to decrease leukemia cell growth by inhibiting mitochondrial transfer and oxidative phosphorylation. (Mistry 2019) The expression of CD38 has also been shown to increase after exposure to ATRA through induction of differentiation through the RARa receptor. (Drach 1994, Buteyn 2018) Targeting AML cells using CD38 has been attempted using DARA *in vitro*. NSG cells were transplanted with T-cell depleted AML and treated with DARA or controls. The treated mice showed a reduction in tumor burden in the spleen and peripheral blood but not bone marrow aspirates. (Dos Santos 2014) This provides a rationale for targeted CD38 in AML.

2.2 Natural Killer Cells

Cancer immunotherapy is a rapidly evolving field that has transformed the treatment of many tumor types, including advanced hematologic malignancies. Key advancements in this field include the development of mAbs that block key inhibitory pathways on T cells, such as those that block programmed cell death receptor-1 (PD-1) and programmed cell death ligand-1 (PD-L1), and the development of adoptive transfer of immune cells as exemplified by chimeric antigen receptor (CAR) T-cell therapy. Both approaches have led to the development of novel therapeutic regimens that have increased survival in patients with a variety of solid and hematopoietic tumors. However, despite these important advances, the majority of patients will either not respond or eventually experience disease relapse. Further understanding of the biology that enables these cells to enter tumors and retain anti-tumor cytotoxic activity is important in order to maximize their clinical benefit for patients.

NK cells are so named for their “natural” ability to kill cancer cells without prior sensitization (Kiessling 1975). NK cells target and kill cancer cells by multiple mechanisms (Figure 3), including direct cytotoxicity, cytokine secretion, and ADCC, which support their clinical investigation in oncologic indications as monotherapy and in combination with mAb therapy as follows:

- Direct cytotoxicity through the targeted release of perforins and granzymes. Importantly, while major histocompatibility complex class I (MHC-I)-deficient cells evade CD8 T-cell recognition, they are preferential targets for NK cells and are highly susceptible to NK-cell-mediated killing (Malmberg 2017).
- Secretion of cytokines, including interferon-gamma (IFNγ) and tumor necrosis factor-alpha (TNFα), promote direct tumor-cell killing (Wang R 2012).

- ADCC, which occurs when an antibody binds to a tumor cell and the antibody's Fc region binds to the CD16 receptor on NK cells, triggering a targeted and engaged cytotoxic response toward the tumor cell (Waldhauer 2008; Wang W 2015).

In addition to direct effects on tumor cells, NK cells can interact with the adaptive immune system to generate and maintain adaptive immune responses against cancer cells as follows:

- Killing of tumor cells by NK cells results in the release of tumor antigens for recognition by the adaptive immune system (Dahlberg 2015).
- Upon activation, NK cells secrete cytokines that recruit and activate endogenous T cells. Importantly, activated NK cells are potent producers of chemokines such as CXCL10, CCL4, and CCL5, which are known recruitment factors for T cells. Cytokines secreted by NK cells also induce maturation of dendritic cells, which serve as antigen-presenting cells to mediate adaptive immune responses (Smyth 2002).

Through these aforementioned mechanisms, NK cells have the intrinsic potential to bridge the innate and adaptive immune response and turn a tumor that is immunologically "cold" to one that is "hot," characterized by an increased immune infiltrate that can potentially restore adaptive immune function.

In clinical investigations, allogeneic NK-cell therapies have been well tolerated with documented anti-tumor activity. More than 500 patients across 30 completed clinical studies have received allogeneic NK cells (Veluchamy 2017). Notably, and unlike allogeneic T-cell therapies, allogeneic NK cells have not been associated with graft-vs-host disease (GvHD). Furthermore, with the exception of NK cells combined with a potent IL-15 agonist (Cooley 2019), allogeneic NK-cell therapies have not been associated with cytokine release syndrome (CRS) or neurotoxicity, which are common complications observed with CAR T-cell therapies. Complete remission rates ranging from 21% to 53% have been observed following a single administration of allogeneic NK cells in subjects with relapsed/refractory (r/r) AML (Miller 2005; Bachanova 2014; Romee 2016), and in subjects with poor prognosis refractory non-Hodgkin lymphoma (Bachanova 2018). Clinical responses have also been reported in subjects with solid tumors, including non-small cell lung cancer (Iliopoulou 2010; Tonn 2013), as well as in subjects with platinum-resistant ovarian cancer (Geller 2011), melanoma (Arai 2008), and renal cell carcinoma (Arai 2008).

2.3 FT538

FT538 is an allogeneic natural killer (NK)-cell immunotherapy produced from a clonal master human-induced pluripotent stem cell (iPSC) line with the following engineered elements: a) deletion of the gene encoding CD38 (i.e., CD38 knockout [KO]; Bjordahl 2019; Cichocki 2019); b) high-affinity, non-cleavable CD16 receptor (hnCD16; Jing 2015; Zhu 2020); and c) interleukin (IL)-15/IL-15 receptor alpha fusion protein (IL-15RF; Rubinstein 2006; Stoklasek 2006). The clonal master cell bank (MCB) used for the production of FT538 was generated by selecting and expanding a single well-characterized iPSC clone in which a single IL15RF/hnCD16 expression cassette was inserted into the CD38 gene locus through non-viral-mediated targeted transgene integration. The use of a clonal MCB as the starting material for routine current Good Manufacturing Practices (cGMP) production of FT538 is intended to directly address many of the limitations associated with patient- and donor-specific cell therapies. Notably, many doses of FT538 drug product can be uniformly produced in a single manufacturing campaign. These doses of drug product are homogeneous and are: (i) tested to assure compliance with a pre-defined quality specification, (ii) cryopreserved in an infusion medium, and (iii) stored to maintain a sustainable inventory. As such, FT538 in the clinical setting has off-the-shelf availability for use in multi-dose regimens, which may prove critical for driving long-term durable responses in patients with progressing disease.

The engineered features of FT538 are designed to result in increased activity against target tumor cells as monotherapy and when combined with monoclonal antibodies (mAbs) that can mediate antibody-dependent cellular cytotoxicity (ADCC). Important functional attributes of FT538 include the following:

- FT538 is expected to have superior effector function compared to patients' endogenous NK cells, which are typically diminished in number and function due to prior treatment regimens (e.g., chemotherapy) and tumor suppressive mechanisms. FT538 mediates "innate cytotoxicity" that is potent and specific to transformed cells.
- The CD38 gene KO in FT538 is intended to prevent anti-CD38 antibody-mediated NK-cell fratricide and consequently enhance ADCC when FT538 is administered with concurrent anti-CD38 mAb therapy (Bjordahl 2019). In addition, NK cells with CD38 KO have been shown to be more resistant to oxidative stress and exhibit enhanced effector function (Cichocki 2019).
- FT538 expresses an hnCD16 Fc receptor. The high-affinity CD16 variant arising from a naturally occurring 158V polymorphism has demonstrated enhanced ADCC when combined with therapeutic mAbs in nonclinical studies. In clinical studies evaluating patients whose endogenous NK cells express the

high-affinity CD16 Fc receptor variant, higher objective response rates and increased progression-free survival (PFS) were observed with treatment with rituximab, cetuximab, and trastuzumab (Cartron 2002; Musolino 2008; Bibeau 2009). In addition, hnCD16 contains the genetic alteration (S179P) that prevents cleavage of CD16 by the metalloproteinase ADAM17 (Lajoie 2014; Jing 2015), a mechanism in the regulation and attenuation of NK-cell activity by the tumor microenvironment (Romee 2013).

FT538 expresses IL-15RF, designed to provide an endogenous activation and proliferation signal, reducing the dependence on exogenous cytokine administration such as IL-2 and IL-15, both of which have been associated with significant toxicities that may limit clinical usage when incorporated into clinical studies of peripheral blood NK cells (Cooley 2019).

These features justify investigation of FT538 in a broad array of oncology indications including, but not limited to, the following:

- As monotherapy, e.g., acute myelogenous leukemia (AML), where FT538 may provide greater clinical benefit than current allogeneic NK-cell-based therapies.
- In combination with approved and investigational tumor-targeting, ADCC-capable mAbs, including daratumumab, which target CD38, and are approved for the treatment of patients with multiple myeloma (MM).

2.4 The Role of Daratumumab and Use of subQ DARZALEX FASPRO

Daratumumab (DARA) is a monoclonal IgG1κ antibody against CD38, a transmembrane glycoprotein with both receptor and enzymatic functions expressed on hematopoietic cells. It was approved by the FDA in 2015 for the treatment of multiple myeloma. DARA binds the CD38 antigen and induces cellular lysis through complement activity, antibody-dependent toxicity, antibody-dependent cellular phagocytosis, and direct apoptosis.

A formulation of daratumumab for subcutaneous administration was developed to shorten the time required to administer daratumumab and to lessen the incidence and severity of infusion related reactions (IRRs) observed with intravenous (IV) daratumumab. A recombinant human hyaluronidase PH20 (rHuPH20) was used to decrease the injection volume required, facilitating the subcutaneous administration of daratumumab. FDA approval DARZALEX FASPRO was received in April 2020 for the treatment of adults with multiple myeloma as a monotherapy and in combination with select standard of care drugs. (DARZALEX FASPRO Prescribing Information)

In a pooled safety population of 490 patients who received DARZALEX FASPRO as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 2: 3.9%, Grade 3: 1.4%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 9 minutes to 3.5 days). Of the 84 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in less than 1% of the patients. (DARZALEX FASPRO Prescribing Information)

2.5 Lymphodepletion with Cyclophosphamide and Fludarabine

The importance of lymphodepleting chemotherapy has been well demonstrated in mouse experiments and was first proposed by the National Cancer Institute (NCI) in the context of melanoma specific CTL by Rosenberg and colleagues. (Dudley 2002) Lymphodepleting conditioning prior to adoptive transfer of lymphocytes is thought to promote persistence of adoptively transferred lymphocytes by creating "immunologic space" and providing a pool of homeostatic cytokines such as IL-15. The use of Cy/Flu-mediated lymphodepletion at the proposed doses and schedule is consistent with our previous human experience. (Miller 2005, Bachanova 2014)

We and others (Buteyn 2018, Dos Santos 2014, Drach 1994) have demonstrated that CD38 is present on hematopoietic cells. The expression on NK cells is in part the rationale for the CD38 knockout in the therapeutic product FT538. However, the proposed therapy plan may have an additional therapeutic advantage to target CD38 expressing regulatory T cells (Treg) and myeloid-derived suppression cells, depletion of which could enhance the anti-tumor activity of immunomodulatory therapies. Thus, the combination of FT538 and Daratumumab is expected to have three therapeutic mechanisms of action in this protocol: 1) to target host immune suppressor cells and enhance NK cell adoptive transfer by enhancing lymphodepletion, 2) direct targeting of CD38 on AML cells and 3) providing the killing mechanism of natural cytotoxicity by which NK cells recognize AML targets independent of antibody dependent cellular cytotoxicity (e.g. through down regulation of MHC class I and upregulates of stress ligands on AML; both increasing recognition and AML killing by NK cells).

For the protocol amendment version dated 24 November 2022: Five patients have enrolled per Stage 1 Step 1 process, 4 have received FT538 with no related G3/4 AEs or DLTs, with most current patient on dose level 4 . However, we have not seen any signal of efficacy. Correlatives drawn to track the expansion of the cells have shown poor expansion. In order to determine factors that may contribute to increased FT538 pharmacokinetics, we have increased the initial lymphodepletion

to reflect a more established regimen that has been previously described as effective with acceptable safety parameters [Miller et al. Blood. 2005].

Amendment March 2023: In the original treatment plan we had hypothesized that multiple doses of daratumumab might allow lower doses of cyclophosphamide and fludarabine (as used in enrollment to date) to prolong the pharmacokinetics of the FT538 NK cell product. However, new information on subjects treated to date shows that FT538 persistence in vivo was not achieved at 14 days even at the highest cell doses, the biomarker goal of the treatment strategy. This was surprising because in our prior work, 14-day persistence was achieved in some subjects in various studies using high-dose cyclophosphamide and 5 days of fludarabine (HiCyFlu). In the November 2022 revision, we increased to HiCyFlu doses previously tested. With this plan, we will decrease to 1 dose of daratumumab as multiple doses are no longer needed to increase persistence. Given the long half-life of daratumumab (approximately 3 weeks), 1 dose is sufficient to mediate ADCC to CD38+ AML targets for the multi-dose FT538 infusion plan while reducing the risk that study participants might develop toxicity requiring management with corticosteroids, which could also compromise FT538 persistence.

2.6 Study Rationale

FT538 is an allogeneic natural killer (NK)-cell immunotherapy produced from a clonal master human-induced pluripotent stem cell (iPSC) line with the following engineered elements: a) deletion of the gene encoding CD38 (i.e., CD38 knockout); b) high-affinity, non-cleavable CD16 receptor (hnCD16); and c) interleukin (IL)-15/IL-15 receptor alpha fusion protein (IL-15RF).

The engineered features of FT538 are designed to result in increased activity against target tumor cells as monotherapy and when combined with monoclonal antibodies (mAbs) that can mediate antibody-dependent cellular cytotoxicity (ADCC). These features justify investigation of FT538 in advanced acute myelogenous leukemia (AML):

- As monotherapy where FT538 may provide greater clinical benefit than current allogeneic NK-cell-based therapies as currently being tested in Fate Therapeutic clinical study FT538-101.
- As proposed in this study use in combination with the tumor-targeting, ADCC-capable mAb, daratumumab, which targets CD38.

2.7 Rationale to Include Pediatric Patients 12 Years Old or Older

Treatment of acute myeloid leukemia (AML) in children has improved remarkably during the past decades; however, pediatric patients with relapsed and refractory AML still have poor outcomes (Kaspers 2014, Zwaan 2015). In fact, the probability of long -term survival in these patients is dismal at around 35%. These outcomes

rely on disease-dependent characteristics which include cytogenetics, timing or relapse, and response to chemotherapy (Pui 2011). Moreover, intensive chemotherapy and allogeneic hematopoietic cell transplantation (HCT) are required for a cure; this can lead to significant morbidity and mortality. Considering poor outcome and high toxicity of current salvage therapies, new treatments are needed.

Daratumumab has been safely and effectively administered to children to treat autoimmune hemolytic anemia after HCT (Schuetz 2018). Based on preclinical efficacy of daratumumab in acute leukemia (Bride 2018, Vogiatzi 2019) as well as case report of clinical efficacy of this agent in child with relapsed leukemia (Ganzel 2018), several clinical trials are now evaluating the safety and efficacy of daratumumab in children with relapsed or refractory leukemia.

Given the dire prognosis of relapsed or refractory AML, and to ensure justice in this research protocol, we have included children ≥12 years of age. We are including children under 45 CFR 46.405 as this research involves greater than minimal risk but presents the prospect of direct benefit to the individual subjects. We have chosen to limit the age of enrolment to children ≥12 years such that assent can be obtained along with the consent of their parents/guardians.

3 Study Design

This Phase I open-label dose escalation study is conducted in two stages with a primary endpoint to identify the maximum tolerated dose (MTD) of FT538 when administered with daratumumab in patients 12 years and older with advanced acute myeloid leukemia (AML) and related myeloid diseases.

FT538 is an off-the-shelf product comprised of allogeneic natural killer (NK)-cell immunotherapy lacking CD38 and expressing hnCD16 and IL-15RF. Daratumumab is a targeted therapy (IgG1k human monoclonal antibody) that targets CD38.

FT538 is administered once a week for 3 consecutive weeks (Day 1, Day 8, and Day 15). There is no Day 0 in this treatment plan. Up to 5 dose levels will be tested. Fixed dose subcutaneous daratumumab is given on Day -5 prior to the FT538 cells as lymphodepletion. A short course of outpatient lymphodepleting chemotherapy is given from Day -6 through Day -3 to promote adoptive transfer.

FT538 dose level cohorts are defined as:

Table 1: Dose Level and Schedule

Dose Level (DL)	Treatment Plan for FT538
-1	5 x 10^7 cells on Day 1, Day 8 and Day 15
1 (start)	1 × 10^8 cells on Day 1, Day 8 and Day 15

Dose Level (DL)	Treatment Plan for FT538
2	3×10^8 cells on Day 1, Day 8 and Day 15
3	1×10^9 cells on Day 1, Day 8 and Day 15
4	1.5×10^9 cells on Day 1, Day 8 and Day 15

The trial is conducted with no intra-patient escalation.

Enrollment on this trial will not begin until all patients on the AML monotherapy Dose Cohort 1 clear the DLT window in the Fate sponsored Protocol FT538-101: FT538 as Monotherapy and in Combination with mAbs in Advanced Hematologic Malignancies. UMN is a participating site in this industry sponsored trial.

Enrollment of pediatric patients (12 years and older) will not begin until a minimum of 6 adults are treated on this study and/or the combination arm on FT538-101 and safety data is submitted to the FDA for their review and permission to proceed with the enrollment of children is received.

This study is performed in two stages, with Stage 1 having two potential steps. A minimum of 28 days separates each patient cohort. A minimum of 14 days must pass between the enrollment of the 1st and the 2nd patient in 3 patient cohorts. All patients are assessed for Dose Limiting Toxicity (DLT) as defined in the Schema and in Section 6.3.1.

STAGE 1 STEP 1 Fast-track design (1 patient per dose cohort)

Start at Dose Level 1 (DL1), enroll 1 patient per dose cohort separated by 28 days (DLT period) until the:

- **1st pre-defined adverse event** defined as any Grade 3 non-hematologic AE within 72 hours of a FT538 infusion
- and the patient completes the 28 day DLT period with no DLT- **Activate Stage 1 Step 2**

OR

- **1st DLT event** within 28 days after the 1st dose of FT538 as defined in the Schema and in Section 6.3.1 - **Activate Stage 2** (Stage 1 Step 2 is not used)

OR

- **10 patients are treated at the Dose Level 4** (This completes enrollment - Stage 1 Step 2 and Stage 2 are not used)
  - If the first patient at dose level 4 in stage 1 step 1 completes DLT period with no pre-defined adverse events or DLT, successive subjects may enroll without staggering.

STAGE 1 STEP 2 Expand current Dose Level and subsequent DLs to 3 patients

The cohort size increases from 1 to 3 patients with 2 additional patients added to the current cohort. A minimum of 14 days must pass between the enrollment of the 1st

and the 2nd patient in 3 patient cohorts and a minimum of 28 days between dose cohorts. Continue dose escalation until:

- **1st DLT event** as defined in the Schema and Section 6.3.1 - **Activate Stage 2**

OR

- **10 patients are treated at the Dose Level 4** (This completes enrollment and Stage 2 is not used.)
  - For Dose Level 4 in stage 1, step 2, second and third patients may enroll immediately but must complete their DLT period prior to enrolling the rest. If no DLT events within monitoring period, successive subjects may enroll without staggering.

STAGE 2 Continual Reassessment Method (CRM) at the 1st DLT

The study design changes to the CRM. Enrollment occurs in cohorts of three. A minimum of 14 days must pass between the enrollment of the 1st and the 2nd patient in 3 patient cohorts. Each new cohort of three patients is sequentially assigned to the most appropriate dose by the study statistician based on the updated toxicity probabilities once the 3rd patient in a cohort reaches Day 29 (end of DLT period). The MTD is identified by the minimum of the following criteria: (1) the total Stage 2 maximum sample size of 25 is exhausted or (2) 10 consecutive patients are enrolled at the same FT538 dose.

The primary analysis for Phase I is intent-to-treat in that all patients receiving the 1st infusion of FT538 are evaluable for toxicity and efficacy. Patients who discontinue therapy prior to the first FT538 will be replaced.

All patients are monitored for dose limiting toxicities (DLTs) and unacceptable toxicity using early stopping rules.

The definition of dose limiting toxicity (DLT) is found in Section 6.3.1.

The definition of excessive toxicity is found in Section 6.3.2.

Follow-up: Direct study participation ends at 1 year after the 1st dose of FT538.

Long-Term Follow-Up for any patient who received at least one dose of FT538: After 1 year, follow-up transfers to a separate long-term follow-up (LTFU) study to continue the FDA's recommended 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 persons 12 of age 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 that of other advanced AML studies at this institution. Refer to Section 4.2.1 of FDA mandated delay in the enrollment of minor patients.

4.1 Disease Specific Inclusion Criteria

Acute myeloid leukemia relapsed/refractory after 2 lines of therapy; with CD38 expression

4.1.1 CD38 expression is defined by ≥20% of malignant cells with CD38 expression by flow cytometry on the most recent marrow biopsy (within 30 days of enrollment – archived or fresh).

4.1.2 Relapsed/refractory is defined as failure to achieve at least a Morphological Leukemia Free State (MLFS) or reverting from MLFS.

4.1.3 Lines of therapy are defined as (must have had 2 prior therapies):

- One cycle of an Intensive induction chemotherapy such as 7+3, 5+2, MEC, FLAG, FLAG-Ida, or CLAG ± small molecule inhibitor
- Four weeks of HMA-based induction ± small molecule inhibitor
- Hematopoietic stem cell transplantation (HSCT), must be >90 days post
- Gemtuzumab Ozogamicin
- LDAC + glasdegib
- Biomarker-specific targeted agents (FLT3 inhibitors, IDH1/2 inhibitors, others if available)
- Other treatments could be considered after discussion with the PI

4.2 Inclusion Criteria

4.2.1 Age 12 years or older at the time of consent - Please note, enrollment of minors will be begin until permission to proceed is received from the FDA. At that time, the protocol will be updated to open enrollment to minors.

4.2.2 Weight ≥ 50 kg due to FT538 fixed cell dosing and FT538 product pre-dose packaging

4.2.3 Karnofsky performance status of 70-100% for 16 years and older or Lansky Play Score of 70-100 for ≥12 and < 16 years of age (refer to Appendix I)

4.2.4 Evidence of adequate organ function within 14 days prior to starting study treatment defined as:

- Estimated Glomerular Filtration Rate (estimated creatinine clearance) ≥50 mL/min/1.73m^2
- Total bilirubin ≤ 5 × upper limit normal (ULN), not applicable for patients with Gilbert's syndrome

- AST ≤3 × ULN and ALT ≤ 3 × ULN, not applicable if determined to be directly due to underlying malignancy

4.2.5 Contraceptive use by men or women

- Female subjects: Women of childbearing potential (WOCBP) must use a highly effective form of contraception from the screening visit until at least 12 months after the final dose of cyclophosphamide (CY), at least 4 months after the final dose of FT538, and at least 4 months after the dose of daratumumab, whichever is latest.
- Male subjects: Males with a female partner of childbearing potential or a pregnant female partner must be sterile (biologically or surgically) or use a highly effective method of contraception from the screening visit until at least 14 months after the final dose of CY and at least 6 months after the final dose of FT538, and at least 5 months after the dose of daratumumab, whichever is latest.

4.2.6 Must agree to and sign the consent for the companion Long-Term Follow-Up study to fulfill the FDA recommended 15 years of follow-up for a genetically modified cell product.

4.2.7 Patient ≥18 years provides voluntary written consent prior to the performance of any research related procedure. Minors (<18 years) provide voluntary written assent with the parent/guardian signing the treatment consent prior to the performance of any research related procedure.

4.3 Exclusion Criteria

4.3.1 Diagnosis of acute promyelocytic leukemia (APL)

4.3.2 Pregnant or breastfeeding, Menstruating females of child-bearing potential must have a negative pregnancy test within 14 days prior to study treatment start

4.3.3 Known allergy to any of study drugs or their components

4.3.4 Clinically significant cardiovascular disease including any of the following: myocardial infarction within 6 months prior to first study treatment; unstable angina or congestive heart failure of New York Heart Association Grade 2 or higher (Appendix II) or cardiac ejection fraction <40%

4.3.5 Any known condition that requires systemic immunosuppressive therapy (> 5mg prednisone daily or equivalent) during the FT538 dosing period (3 days before the 1st dose through 14 days after the last dose) excluding pre-medications – inhaled and topical steroids are permitted

4.3.6 Receipt of any biological therapy, chemotherapy, or radiation therapy, except for palliative purposes, within 2 weeks prior to Day 1 or five half-lives, whichever is shorter; or any investigational therapy within 28 days prior to the to the first dose of daratumumab.

4.3.7 Known active central nervous system (CNS) involvement or treated CNS disease that has not cleared. If prior disease related CNS involvement must have completed effective treatment of their CNS disease at least 2 months prior to Day 1 with no clinical evidence of disease

4.3.8 Non-malignant CNS disease such as epilepsy, CNS vasculitis, or neurodegenerative disease or receipt of medications for these conditions in the 2-year period leading up to study enrollment

4.3.9 Clinically significant untreated/uncontrolled infection

4.3.10 Live vaccine <6 weeks prior to start of lympho-conditioning

4.3.11 Known seropositive for HIV or known active Hepatitis B or C infection with detectable viral load by PCR

4.3.12 Prior solid organ transplant

4.3.13 Allogeneic HSCT within previous 90 days

4.3.14 Active graft-versus-host-disease (GvHD) requiring systemic immune-suppression within 14 days prior to enrollment

4.3.15 Presence of any medical or social issues that are likely to interfere with study conduct or may cause increased risk to the participant.

5 Patient Screening and Enrollment

5.1 Registration with the Masonic Cancer Center Clinical Trials Office

Any patient who is consented is to be entered 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.

5.2 Patient Enrollment and Dose Cohort Placement

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. The patient is placed in the currently enrolling dose cohort.

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 FT538, 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 at least 1 dose of FT538, they are considered on treatment and must continue follow-up per Section 8.

6 Treatment Plan

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.). In this study, hydroxyurea may be used at any time to control peripheral blood blasts.

Because they may inhibit NK cell function, additional systemic corticosteroids should be avoided unless absolutely required. Standard pre-medications for study drugs (including corticosteroids as daratumumab pre-meds) are permitted.

There is some flexibility in the timing of the treatment as long as the ordering of the treatment is maintained and a minimum of 48 hours separates the last dose of fludarabine and the 1st FT538 infusion. The below Table 1 represents the treatment plan when Day 1 is a Monday and treatment is given as planned.

Table 1. Treatment Plan Example with Day 1 = Monday

Study Day	Day of Week	Agent	Protocol Section
Day – 6	Tuesday	FLU	Section 6.2
Day -5	Wednesday	Daratumumab, FLU	Section 6.1, Section 6.2
Day -4, Day -3	Thursday, Friday	CY/FLU	Section 6.2
Day -2	Saturday	FLU	Section 6.2
Day 1	Monday	FT538	Section 6.3
Day 8	Monday	FT538	Section 6.3
Day 15	Monday	FT538	Section 6.3

There is no Day 0 in this treatment plan.

6.1 Daratumumab Administration Guidelines

Daratumumab subQ 1800 mg co-formulated with 30,000 units of hyaluronidase (rHuPH20) into the subcutaneous tissue of the abdomen approximately 3 inches [7.5 cm] to the right or left of the navel over approximately 3-5 minutes on Day -5 prior to the 1st FT538 infusion.

- Never inject DARZALEX FASPRO into areas where the skin is red, bruised, tender, hard, or areas where there are scars.

- Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by pausing or slowing down delivery rate, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.
- During treatment with DARZALEX FASPRO, do not administer other medications for subcutaneous use at the same site as DARZALEX FASPRO.

Pre- and Post-Medications:
Administer the following pre-medications 1-3 hours before daratumumab:

- Acetaminophen 650 to 1,000 mg orally
- Diphenhydramine 25 to 50 mg (or equivalent) orally or intravenously
- Methylprednisolone 60 mg (or equivalent) orally or intravenously. Dose Day -5 and Day -4.

Refer to Section 2.4 for injection related reaction presented in the current Investigator Brochure. With the subcutaneous route, in a pooled safety population of 490 patients who received DARZALEX FASPRO as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 2: 3.9%, Grade 3: 1.4%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections.

For patients with a history of chronic obstructive pulmonary disease, consider prescribing short and long-acting bronchodilators and inhaled corticosteroids. F

Prophylaxis for Herpes Zoster Reactivation:
Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting DARZALEX FASPRO and continue for 3 months following the end of treatment.

Monitoring:
Monitor patients for systemic administration-related reactions and localized injection site reaction.

A recommended post-injection observation is 3.5 hours with vital signs documented prior to the injection and post injection per institutional standards.

For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the

administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Subcutaneous administration of daratumumab may be associated with a local injection site reactions, such as induration and erythema. The reactions usually resolved within 60 minutes. Local injection site reactions should be managed per institutional standards.

DARZALEX FASPRO dose reductions are not recommended. Skipped or delayed dosing is permitted.

6.2 Cyclophosphamide/Fludarabine Lymphodepletion Guidelines

A lymphodepleting regimen of fludarabine and cyclophosphamide is given in the outpatient clinic on 5 consecutive days (Day -6, Day -5, Day -4, Day -3 and Day -2).

The administration of the preparative regimen will follow the institutional dosing guidelines. Dose and/or schedule adjustments consistent with the standard of care may be made on an individual patient basis as needed for safety.

Fludarabine 25 mg/m^2 is administered as a 1 hour intravenous (IV) infusion per institutional guidelines once a day on 5 consecutive days (Day -6, Day -5, Day -4, Day -3 and Day -2).

Cyclophosphamide 60 mg/kg is administered as a 2 hour intravenous infusion per institutional guidelines once a day on Day -4 and Day -3.

Cyclophosphamide dosing is calculated based on ABW (Actual Body Weight) unless ABW is >150% of the IBW (Ideal Body Weight).
Adjusted body weight = IBW + 0.5(ABW-IBW).

Cyclophosphamide associated hydration will be given according to recommended institutional standards.

6.3 FT538 Administration

FT583 is given in the same manner for all patients treated on this study. Refer to Section 3 for the study design/enrollment plan.

FT538 will be provided by Fate Therapeutics as cryopreserved dose specific bags and stored at the Molecular Cellular Therapy (MCT) Laboratory until needed. FT538 is thawed on the unit prior to administration.

FT538 is administered as an IV infusion via gravity using an IV administration set with an in-line filter at the patient's assigned dose levels on Day 1, Day 8, and Day 15. Refer to Table 2 below.

Table 2: FT538 cell product dose levels (bag requirements)	
Dose Level	FT538 cells
-1	5×10^7 FT538 cells/dose (1 bag at 5×10^7 cells/bag)
1 (start)	1×10^8 FT538 cells/dose (1 bag at 1×10^8 FT538 cells/bag)
2	3×10^8 FT538 cells/dose (3 bags at 1×10^8 FT538 cells/bag)
3	1×10^9 FT538 cells/dose (2 bags at 5.0×10^8 FT538 cells/bag)
4	1.5×10^9 FT538 cells/dose (3 bags at 5.0×10^8 FT538 cells/bag)

Dosing is based on hnCD16 expression, where 90%±10% of FT538 cells express hnCD16.

FT538 Thawing Overview: FT538 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. FT538 is stable for up to 60 minutes post-thaw. Administration of the cell product must begin within 60 minutes of thawing.

FT538 Infusion guidelines: FT538 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.

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 FT538 and 4-6 hours later, patients should receive acetaminophen 650 mg orally (PO) and diphenhydramine 25 PO. Corticosteroids should not be used as pre-medication for FT538.

Vital Signs: Vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiration rate) are performed in association with the FT538 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 FT538.

Collection of research sample 30 (±5) minutes after the last bag of FT538 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 FT538 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 receives supportive care per Section 7.1 guidelines. The patient will receive no further FT538.

All patients are monitored for adverse events, dose limiting toxicity, stopping rule events, and death per Section 10.

Refer to Section 7 for management of FT538 related toxicity.

6.3.1 Dose Limiting Toxicity

Dose limiting toxicity (DLT) is defined as any AE (based on CTCAE v5) that is at least possibly related to FT538 and not related to disease progression that occurs after the first FT538 infusion through the end of the DLT assessment period on Day 29 as defined below:

Table 3: Definition of Dose Limiting Toxicity	
Dose Limiting Toxicity (DLT)	Exceptions
• Any Grade 4 non-hematologic AE	• Fever associated with CRS that occurs in the context of Grade <3 CRS
• Grade 3 pulmonary or cardiac AE of any duration • Grade 3 immune cell associated neurotoxicity syndrome (ICANS) of any duration • Any other Grade 3 non-hematologic AE of >72 hours duration*	• Grade 3 renal or hepatic AE lasting < 7 days • Grade 3 fatigue lasting ≤ 3 days • Grade 3 laboratory abnormality, unless otherwise specified that is asymptomatic and not clinically significant
• Grade ≥2 acute GvHD requiring systemic steroid administration	

* Note: Febrile neutropenia is not a hematologic AE or laboratory abnormality

6.3.2 Monitoring for Excessive Toxicity

All patients receiving the FT538 cell product will be monitored for unacceptable toxicity using early study stopping rules (SR). The following events are considered excessive toxicity per Section 12.4.

- Excessive treatment emergent adverse events that meet DLT criteria within the DLT period - The trial will be stopped if the posterior probability that the lowest dose is unacceptably toxic (> 25% of patients) is greater than 80%;
- Grade 4 or greater FT538 infusion related reaction;
- Aplasia at Day 42 (ANC <500) after at least 1 week of growth factor (i.e. G-CSF) with an aplastic bone marrow in the absence of leukemia (<5% cellularity);
- Any death within 28 days after the last dose of FT538 and not attributable to disease progression.

6.4 Permitted and Prohibited Concomitant Medications/Therapies

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.). Growth factor should be avoided until 3 days after the last dose of FT538 unless medically indicated. If at Day 29, bone marrow recovery is delayed, growth factor (i.e. G-CSF) should be initiated. Aplasia at Day 42 after at least 1 week of GF is considered excessive toxicity as detailed in Section 6.3.2.

At the treating investigator's discretion, hydroxyurea may be used at any time to control peripheral blood blasts and/or white blood count. Although classified as a chemotherapy, in this situation it is considered suppressive only and part of supportive care as it has no impact on actual disease blasts. Consequently, the use of hydroxyurea would not affect a patient's evaluability for response and toxicity.

Systemic corticosteroids should be avoided during the treatment cycle, unless absolutely required, because they may inhibit NK-cell function. Because of their deleterious effect on NK-cell-based therapy, corticosteroids as pre-medication should be avoided unless considered necessary by the investigator and should not be administered within 24 hours before or after FT538 administration. Guidelines regarding the use of corticosteroids for daratumumab for injection-related reaction prophylaxis are described in Section 6.1.

Long-acting corticosteroids, such as dexamethasone, should not be used as pre-medication for FT538 infusion-related reaction prophylaxis.

Prohibited therapies include any antineoplastic agent for therapeutic intent other than protocol-directed study treatment while on study treatment.

6.5 Duration of Treatment

Treatment consists of a single course of treatment over approximately 5 weeks unless unacceptable toxicity, rapidly progressing disease, patient refusal, or the treating investigators feels treatment is not in the best interest of the patient.

An End of Treatment (EOT) assessment occurs at Day 29 to confirm no ongoing side effects/toxicity related to study treatment. If ongoing toxicity, it should be managed as medically appropriate and documented, it if meets the criteria for documenting as an AE be followed until resolution or stabilization.
Patients are monitored for unacceptable toxicity using early study stopping rules (SR) through Day 42.

Any patient receiving at least one dose of FT538 is followed per Section 8.1 and on the Long-Term Follow-Up protocol per Section 6.7.

6.6 Follow-Up for Disease Response and Survival (Duration of Study Participation)

Patients are followed for disease response until disease progression/relapse and then survival until the end of the 12 month follow-up period (from the 1st dose of FT538).

Follow-up assessments may be in person, by medical record review, or local medical doctor if patient is no longer seen at the treating institution. In person follow-up visits solely for this research study are not required and may be linked with a standard of care visit. Refer to Section 8 for allowable time related windows around each follow-up time points.

Follow-up may end early if any of the following apply:

- consent is withdrawn
- patient did not receive FT538 – if a patient is not evaluable, follow only until the resolution or stabilization of treatment related toxicity
- new anti-cancer treatment is started (follow for survival only)
- patient is discharged to hospice (terminal) care

If a person ends follow-up before the 12 months study period (i.e. withdraws consent, lost to follow-up), public records will be searched for survival information for the survival endpoint.

Any patient receiving at least 1 dose of FT538 must be followed for up to 15 years per a separate long-term follow-up protocol for late effects and survival regardless of status on the treatment protocol per Section 6.7.

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

FT538 is an engineered cellular immunotherapy product and the long-term safety risk is not known and may include conditions with delayed onset relative to FT538 administration. Specific conditions potentially related to engineered cellular immunotherapy products such as FT538, 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.

This LTFU reporting requirement is fulfilled through a separate study. Consent to the LTFU study is obtained at the time of consent for the treatment study and a condition for eligibility to receive treatment. If a patient does not receive FT538, follow-up on the LTFU study is not relevant. Refer to the LTFU protocol for withdrawal procedures.

7 Recommended Management Guidelines for Specific Adverse Events Associated with FT538

Refer to Section 6.1 for management of daratumumab injection related reactions and Section 9.2.7 for potential risks.

Refer to Appendix III for potential toxicities for the cyclophosphamide and fludarabine.

No FT538 clinical data are available. For this reason:

1) Enrollment of adult patients on this trial will not begin until all patients on the AML monotherapy Dose Cohort 1 clear the DLT window in the Fate sponsored Protocol FT538-101: FT538 as Monotherapy and in Combination with mAbs in Advanced Hematologic Malignancies. UMN is a participating site in the industry sponsored trial.
2) Enrollment of pediatric patients (12 years through 17 years) will not begin until a minimum of 6 adults are treated on this study and/or the combination arm on FT538-101 and safety data is submitted to the FDA for their review and permission to proceed with the enrollment of children is received.

The long-term safety risk is not known and may include conditions with delayed onset relative to FT538 administration.

Suggested guidelines for the management of specific AEs are outlined below.

Dose and schedule modifications of FT538 for AEs are as follows:

- If a Grade 3 or Grade 4 DLT is observed, then the subsequent FT538 infusions could be omitted.
- If a Grade 3 non-hematologic AE that is not a DLT is observed and recovers to baseline by the subsequent scheduled FT538 infusion, then FT538 could be dose-reduced to at least one lower dose level.
  - Dose reduction will not be required for Grade 3 laboratory abnormalities that are not clinically significant
- If a Grade 3 non-hematologic AE that is not a DLT is observed and ongoing at the time of the subsequent scheduled FT538 infusion, FT538 infusion will be delayed until resolution of the AE to baseline, at which time FT538 could be dose-reduced to at least one lower dose level.
  - Dose reduction will not be required for Grade 3 laboratory abnormalities that are not clinically significant
  - For AEs occurring after the first FT538 infusion:
    - If recovery to baseline is not observed by Day 8, the scheduled Day 8 FT538 infusion could be skipped.
    - If recovery to baseline is observed by Day 15, the scheduled Day 15 FT538 infusion may be administered.
    - If recovery to baseline is not observed by Day 15, the scheduled Day 15 FT538 infusion will be skipped.
  - For AEs occurring after the second FT538 infusion, if recovery to baseline is not observed by Day 15, the scheduled FT538 infusion will be skipped.

- If a Grade 3 hematologic AE that is not a DLT is observed, then FT538 dosing will continue according to schedule and without dose modification.
  Additional modifications to the FT538 dosing schedule, including dosing delays, will be based on consultation between the investigator and the principle investigator. (Note: Given the extremely high incidence of febrile neutropenia is patients with relapsed/refractory AML, febrile neutropenia will not be recorded as a hematologic AE; grade 3 febrile neutropenia falls into the same category as "Any other Grade 3 non-hematologic AE" per the table in section 6.3.1)

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 FT538

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 FT538 administration is described below.

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

Stop FT538 administration. Do not restart.

The volume of FT538 administered prior to the infusion-related reaction must be documented; retain any remaining product and contact Dr. Maakaron 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 FT538 administration.
- Manage symptoms, e.g., with antihistamines, antipyretics and analgesics, according to standard institutional practice standards.
- Resume FT538 administration only upon complete resolution of the infusion-related reaction and at the discretion of the Investigator. Given that FT538 administration may involve single or multiple bags depending on the total planned dose and accounting for the stability of FT538 post-thaw, FT538

administration may continue following resolution to a Grade 1 infusion-related reactions as follows:

If single-bag FT538 dosing:

- No additional FT538 may be administered.
- The volume of FT538 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 FT538 that was not administered from the bag during which the infusion-related reaction occurred.

If multiple-bag FT538 dosing:

- The volume of FT538 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 FT538 bags was planned, they may be thawed and administered.
- Additional bags beyond what was originally planned may not be administered to make up for FT538 that was not administered from the bag during which the infusion-related reaction occurred.

7.2 DMSO Related Risks

FT538 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. It is recommended patients receive IV hydration with normal saline (NS) 250 ml bolus before and 250 ml bolus after FT538 administration to reduce the potential risks associated with DMSO.

7.3 Infection

FT538 is cell therapy of human origin. During processing, the cells are in contact with reagents of animal origin, and FT538 has a final formulation which contains albumin (human). As with any product of human and/or animal origin, transmission of infectious disease and/or disease agents by known or unknown agents may occur. FT538 has been extensively tested to minimize the potential risk of disease transmission. However, these measures do not completely eliminate the risk. For

some infectious agents, there are no routine tests to predict or prevent disease transmission (AABB 2016).

7.4 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 in the clinical laboratory, 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 Table 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 deviation.

Management of CRS should follow the recommended management algorithm provided in Table 4 (Neelapu 2018) and/or institutional practice.

Table 4: 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.

Table 4: Recommendations for the Management of Cytokine Release Syndrome		
Grade	Sign/Symptom	Management
		• 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 • 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.

Source: Neelapu et al. 2018; Actemra USPI

7.5 Neurotoxicity

Neurotoxicity must be monitored at the time points specified in the Section 8 using the ASTCT guidelines for grading ICANS (Table 10; Lee et al. 2019) based on the ICE score.

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 5: 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
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 6, Table 7, and Table 8) and/or institutional practice.

Table 6: 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 7 • 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 • 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 8 • 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 7 • Stage ≥3 papilloedema, with a CSF opening pressure ≥20 mmHg or cerebral oedema, should be treated as per algorithm in Table 8

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 7: 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 • 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 8: 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 6) • 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 • 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.

7.6 Acute Graft-versus-Host Disease

Because FT538 is an allogeneic immune effector cell product, there is a potential risk of GvHD even though allogeneic NK-cell therapies have not been associated with GvHD. (Veluchamy 2017).

Acute GvHD assessments will be performed with assignment of the overall severity based on the CIBMTR acute GvHD grading scale (Table 9). Management of GvHD should be done in accordance with local institutional practice.

Acute GvHD will be assessed according to criteria established by the CIBMTR Scale (Table 9).

Management of GvHD should be done in accordance with local institutional practice.

Table 9: GVHD Grading and Staging

Source: https://www.cibmtr.org/manuals/fim/1/en/topic/f2100-q131-233, assessed Oct 20, 2020.

Extent of Organ Involvement			
Stage	**Skin**	**Liver**	**Gut**
1	Rash on <25% of skin[1]	Bilirubin 2-3 mg/dl[2]	Diarrhea > 500 ml/day[3] or persistent nausea[4] *Pediatric*: 280-555 ml/m²/day or 10-19.9 mL/kg/day
2	Rash on 25-50% of skin	Bilirubin 3-6 mg/dl	Diarrhea >1000 ml/day *Pediatric*: 556-833 ml/m²/day or 20-30 mL/kg/day
3	Rash on >50% of skin	Bilirubin 6-15 mg/dl	Diarrhea >1500 ml/day *Pediatric*: >833 ml/m²/day or > 30 mL/kg/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dl	Severe abdominal pain, with or without ileus, and / or grossly blood stool
Grade[5]			
I	Stage 1-2	None	None
II	Stage 3	Stage 1	Stage 1
III	—	Stage 2-3	Stages 2-4
IV[6]	Stage 4	Stage 4	—

[1] Use “Rule of Nines” (see Percent Body Surfaces table below) or burn chart to determine extent of rash.

[2] Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

[3] Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Downgrade one stage if an additional cause of diarrhea has been documented.

[4] Persistent nausea with or without histologic evidence of GVHD in the stomach or duodenum.

[5] Criteria for grading given as minimum degree of organ involvement required to confer that grade.

[6] Grade IV may also include lesser organ involvement with an extreme decrease in performance status

7.7 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 autologous stem cell transplant 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.

7.8 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.

7.9 Immunogenicity

It is possible that FT538 may induce an immune response, which may manifest only through laboratory assessments, or may manifest clinically, e.g., as infusion-related reactions with varying degrees of severity, including serious life-threatening anaphylactic reactions. AEs arising from FT538 immunogenicity will be managed per institutional practice.

8 Schedule of Treatment, Tests, and Procedures

"Clinic visits" may be done by a virtual visit or by phone, email, or text to assess general status, review lab results, and any ongoing adverse events.

A minimum of 48 hour must separate the last dose of FLU and the FT538 infusion. There is no Day 0 in this treatment schema.

A ± 1 Day window is permitted for the FT538 infusion to permit some flexibility of scheduling for individual patients.

A ± 1 Day window is permitted for visits until the End of Treatment (EOT) assessment; however, whenever feasible do not shift subsequent future time points off of the targeted day.

The End of Treatment assessment occurs no sooner than Day 29 (+3 days) as this is coincides with the end of DLT period.

After Day 29, follow-up assessments are associated with the closest standard of care visit. The Day 42 follow-up is the final monitoring for excessive toxicity.

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

8.1 Required Clinical Care Evaluations

Bold – investigational agent treatment day Light – Daratumumab Bold shade – FT-538	Screening / Baseline	Day -6	**Day -5**	Day -4	Day -3	Day -2	**Day 1**	Day 2	**Day 3**	**Day 8**	**Day 15**	Day 22	Day 29 EOT/ end of DLT	Day 42 (~end of SR period)	3, 6, 9, and 12 months from 1st FT538 infusion[7]
Consent	X[1]														
Screening Assessment	X														
Brief Medical Assessment			X				X	X		X	X	X	X		
Medical History	X														X
Concomitant Medications[10]	X		X				X		X				X		
Assess Venous Access	X														
Physical Exam	X	X	X	X	X	X									X
Daratumumab			X												
Fludarabine		X	X	X	X	X									
Cytoxan				X	X										
FT-538							X			X	X				
Prophylaxis for Herpes Zoster Reactivation	X (start per Section 6.1)														
ICANS (neurotoxicity)[6] monitoring – refer to Section 7.5							X	X		X	X	X	X		X
KPS or Lansky Play score	X														
Weight	X			X											
Height	X														
Vitals and Pulse Oximetry	X		X				X[5]	X	X	X[5]	X[5]	X[5]	X		
Toxicity Assessment in person or patient reported and survival status	X		X				X	X		X	X	X	X	X	X
CBC, diff, plt	X		X				X	X		X	X	X	X	X	X
Basic metabolic panel (BMP)[1]								X							
Comprehensive metabolic panel (CMP)[2] plus mg, phos	X[9]		X				X			X	X	X	X	X	X
eGFR	X														
Urine or serum pregnancy test for WOCBP[3]	X														
If CRS is suspected or diagnosed							X								
If patient develops neurotoxicity							X[11]								
Disease staging[8]	X											X†			Per SOC
Bone marrow aspirate									X						
CXR or chest CT scan	X														

Bold – investigational agent treatment day Light – Daratumumab Bold shade – FT-538	Screening / Baseline	Day -6	**Day -5**	Day -4	Day -3	Day -2	**Day 1**	Day 2	**Day 3**	**Day 8**	**Day 15**	Day 22	Day 29 EOT/ end of DLT	Day 42 (~end of SR period)	3, 6, 9, and 12 months from 1st FT538 infusion[7]
PFTs[4]	X														
LVEF by echo or MUGA	X														
SOC of assessment for history or suspected CNS involvement per Section 4.3.7	X														

1 basic metabolic panel consists of BUN, creatinine, calcium, glucose, lytes (CO2, Cl, Na, K)
2 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
3 women of child bearing potential – negative test must be obtained within 14 days prior to dose of daratumumab
4 pulmonary function testing required only if symptomatic or prior known impairment
5 Vital signs (temperature, systolic and diastolic blood pressure, heart rate, and respiration rate) are performed in association with the FT538 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 FT538.
6 If on a treatment day, assess 2-4 hours post treatment. 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 7.5. In addition, quantitative testing in blood for HHV6 and HHV7 in the context of neurotoxicity should be done.
7 Long-term follow-up continues for up to 15 years
8 BM aspirate/biopsy with flow, cytogenetics, NGS, and targeted molecular diagnostics. At time of each SOC BM bx collect research related aspirate sample in a green top tube – to TTL † BM aspirate and biopsy for response assessment should be performed on day 25 +/- 4 days.
9 Labs for eligibility per Section 4.2.4 must be done within 14 days prior to daratumumab.
10 Hydroxyurea as used in the study is considered supportive care per Section 6.4, not as an anti-cancer agent
11 ICANS assessments will only be required in the follow up period if clinically indicated, and may be discontinued upon patient's return to baseline.

8.2 Research Related Tests and Procedures

	Baseline prior to study treatment	Prior to DARA D-5	During FT538/DARA					Day 22	End of treatment Visit (end of DLT period) Day 29	End of excess toxicity period ~Day 42	3, 6, 9 and 12 months from 1st dose of FT538 at time of SOC visit
			Prior to FT538 #1 Day 1	Day 2	Day 3	Prior to FT538 #2 Day 8	Prior to FT538 #3 Day 15				
ferritin, CRP (to hospital lab charge to research)[1]	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[2]	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 (10 mL)
One 10 ml green top tube[2] 30 (± 5) minutes post FT538 infusion end			X (post FT538)			X (post FT538)	X (post FT538)				
One 10 ml green top tube[2]				X	X						
Baseline 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										
Safety follow-up: 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 (at 3, 6, and 12 months only)
At time of each bone marrow biopsy and/or aspirate, collect aspirate sample in a green top tube for research	X				X[3]			X[4]			X
PRA anti-HLA antibodies one 10 ml red top (to hospital lab charge to research)	X								X		

Note: enrollment to this study is for patients 50 kg or greater. Adjustment to research blood volumes (weight based) is not required for pediatric patients.
1 - refer to Section 8.1 and Section 7.4 for at the time CRS is suspected and if definitive diagnosis is made
2 - At TTL: PBMCs are isolated from the heparin/green tube for PCR testing by Fate.
3 - ±1 day, must follow FT538 infusion
4- BM biopsy for disease assessment to occur on day 25±4 days.

All research samples go to the Masonic Cancer Center's Translational Therapy Lab (TTL) except for the baseline and Day 29 sample for ferritin and CRP testing and the pre- and post- PRA anti-HLA antibodies samples which are charged to research but run in the treatment center's clinical lab.

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, research samples may be collected at up to 3 extra 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.

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.

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).

Any remaining PBMC will be cryopreserved in 10% DMSO and stored in liquid nitrogen for future testing, if the patient agreed to future storage at the time of initial consent.

9 Study Agents

9.1 FT538

FT538 is an investigational product and can only be used and administered under an FDA-approved protocol. For the purposes of this study FT538 is provided by Fate Therapeutics.

9.1.1 Availability

FT538 will be supplied by Fate Therapeutics for the purpose of this study.

9.1.2 Product Labelling

FT538 labeling will include product name, volume, manufacturer, date of manufacture, Product Lot #, Bag ID #, and amount of VC. The label will also contain the following statement: “Caution: New Drug – Limited by United States Law to Investigational Use.”

9.1.3 Storage

FT538 is stored at the University of Minnesota Molecular and Cellular Therapeutics (MCT).

FT538 must be stored in the vapor phase of liquid nitrogen (VPLN2) at ≤ -150°C, in a continuously temperature-monitored and alarmed VPLN2 freezer in a controlled-access room with limited personnel access. Temperature excursions up to -135°C for 10 minutes due to normal equipment use (e.g., opening and closing of the storage unit) are allowed.

9.1.4 How Provided

The formulated drug product is aseptically filled into pre-sterilized, single-use cryopreservation bags.

9.1.5 Route of Administration

FT538 is thawed and administered as an IV infusion via gravity. The following are acceptable forms of IV access in order of preference:

1. Central venous catheter (CVC; e.g., Hickman)
− Do not use implanted ports.
2. Non-valved peripherally inserted central catheter (PICC)
3. Large-bore (18-gauge) straight IV needle

9.1.6 Potential Toxicities

Refer to Section 7 for potential toxicities.

Refer to the current FT538 Investigator Brochure for additional information.

9.2 Daratumumab

9.2.1 Other names

DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

9.2.2 Description

DARZALEX FASPRO is a combination of daratumumab, a CD38-directed cytolytic antibody, and hyaluronidase, an endoglycosidase

9.2.3 FDA Approved Indications

DARZALEX FASPRO is approved for the treatment of adult patients with multiple myeloma (April 2020).

9.2.4 Availability

A commercial formulation of daratumumab is purchased through the site's Investigational Pharmacy for this study.

9.2.5 How Supplied and Storage

DARZALEX FASPRO (daratumumab and hyaluronidase-fihj) injection is a sterile, preservative-free, colorless to yellow, and clear to opalescent solution for subcutaneous use supplied as individually packaged single-dose vials providing 1,800 mg of daratumumab and 30,000 units of hyaluronidase per 15 mL (NDC 57894-503-01).

Store DARZALEX FASPRO vials in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF) in the original carton to protect from light.

Do not freeze or shake.

9.2.6 Preparation and Administration

DARZALEX FASPRO is ready to use.

- Remove the DARZALEX FASPRO vial from refrigerated storage [2°C to 8°C (36°F to 46°F)] and equilibrate to ambient temperature [15°C to 30°C (59°F to 86°F)]. Store the unpunctured vial at ambient temperature and ambient light for a maximum of 24 hours. Keep out of direct sunlight. Do not shake.
- Withdraw 15 mL from the vial into a syringe.
- DARZALEX FASPRO is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles. Use the product immediately.
- After the solution of DARZALEX FASPRO is withdrawn into the syringe, replace the transfer needle with a syringe closing cap. Label the syringe appropriately to include the route of administration per institutional standards. Label the syringe with the peel-off label.
- To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if opaque particles, discoloration or other foreign particles are present.

Storage of prepared syringe:

- If the syringe containing DARZALEX FASPRO is not used immediately, store the DARZALEX FASPRO solution for up to 4 hours at ambient temperature and ambient light. Discard after 4 hours, if not used.

Administration:

- Inject 15 mL DARZALEX FASPRO into the subcutaneous tissue of the abdomen approximately 3 inches [7.5 cm] to the right or left of the navel over approximately 3-5 minutes. No data are available on performing the injection at other sites of the body.
- Rotate injection sites for successive injections.
- Never inject DARZALEX FASPRO into areas where the skin is red, bruised, tender, hard or areas where there are scars.
- Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by pausing or slowing down delivery rate, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.
- During treatment with DARZALEX FASPRO, do not administer other medications for subcutaneous use at the same site as DARZALEX FASPRO.

9.2.7 Potential Toxicities

Warnings and Precautions:

- Hypersensitivity and Other Administration Reactions: Permanently discontinue DARZALEX FASPRO for life-threatening reactions.
- Neutropenia: Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO to allow recovery of neutrophils.
- Thrombocytopenia: Monitor complete blood cell counts periodically during treatment. Consider withholding DARZALEX FASPRO to allow recovery of platelets.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception. Males and females should use effective contraception for at least 3 months after the last dose of drug.
- Interference with cross-matching and red blood cell antibody screening: Type and screen patients prior to starting treatment. Inform blood banks that a patient has received DARZALEX FASPRO.

Potential Risks:

May be serious

- Serious allergic reactions and other severe injection-related reactions.

- Injection site reactions
- Decrease in blood counts
- Changes in blood type testing for up to 6 months after last dose.

The most common side effect when used as monotherapy included cold-like symptoms (upper respiratory infection).

10 Adverse Event Monitoring, Documentation, and Reporting

For the purposes of the study the FT538 and daratumumab are considered investigational products.

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).

Table 10: 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.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

Adverse Reaction: Any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse event meeting that meets the definition of serious for which there is a reasonable possibility that the drug caused the adverse event and it meets the definition of unexpected.

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
- An important medical event

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.

Note: refer to the current FT538 Investigator Brochure for expected adverse events. For DARZALEX FASPRO™ the current USPI for expected adverse events.

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

10.2 AE Monitoring and Event Documentation Requirements

Adverse event documentation for the purposes of this study will focus on events felt to be related to FT538, daratumumab, or events that cannot be attributed to other causes (i.e., disease under treatment, co-morbidities). Adverse events can be observed in person, abstracted from the medical record or patient reported.

Between the time of consent signing and the start of daratumumab, only events directly related to the study and result in the inability to begin study treatment are documented. Refer to Section 5.3 for handling of patients unable to begin study treatment.

Monitoring for adverse events begins with the first dose of fludarabine on day -6. Frequent monitoring continues through the DLT period until Day 42 or 28 days after the last dose of FT538, whichever is later, based on the definition of excessive toxicity (stopping rules (SRs)). Once beyond the SR period, 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 FT538 will be documented upon knowledge.

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

- expected toxicities felt to be related to daratumumab
- expected toxicities felt to be related to the FT538
- events meeting the definition of a DLT or excessive toxicity per Section 10.4
- any event meeting the definition of serious, regardless of attribution
- unexpected adverse events that cannot be attributed to the disease under treatment

For the purposes of this study, adverse event documentation requirements in OnCore will be based on grade, expectedness and relationship to the investigational product (FT538, daratumumab):

	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

Exceptions to AE Documentation: Laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) without clinical significance are not recorded as AEs or SAEs with the exception of abnormalities that meet the definition of DLT per Section 6.3.1. Other abnormal assessments (e.g., vital signs, ECG, X-rays) that are not associated with signs or are considered of no clinical significance do not need to be recorded unless they are a dose limiting toxicity.

Clinically significant is defined as requiring medical or surgical intervention or leading to a study treatment delay or discontinuation. Any laboratory or other assessments meeting the definition of clinically significant must be recorded as an AE, as well as an

SAE, if applicable. Electrolyte replacement and similar routine supportive care is excluded from AE reporting unless it meets the definition of a DLT.

10.3 SAE Documentation and Reporting

Any event meeting the definition of an SAE must be documented using the MCC SAE Report Form, save for subject death due to disease (see section 10.5)

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

All patients are monitored for dose limiting toxicity (DLT) and excessive toxicity (early stopping events). Refer to Section 6.3.1 and Section 6.3.2 for definitions.

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 10.3.

10.5 Documentation of Death and Reporting Requirements

Deaths during the treatment and follow-up period that are not due to AML will be recorded as an SAE and reported per Section 10.6. Deaths due to patient's underlying disease need not be recorded as SAEs, but should be recorded as a grade 5 neoplasm in the AE log.

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 Expedited MCC Reporting Requirements

As the study sponsor, the Masonic Cancer Center has the following expedited reporting responsibilities:

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 not related to primary malignancy; 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 Fate Therapeutics within 1 business day of FDA reporting pv@fatetherapeutics.com
	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
Fate Therapeutics	Suspected Unexpected Serious Adverse Reactions (SUSARs)	Within 3 business days of knowledge	MCC SAE Report Form	Fate Therapeutics at pv@fatetherapeutics.com
	All other SAE's	Within 5 business days of knowledge		

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/dsmp

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.

IND Annual Reports

In accordance with regulation 21 CFR § 312.33, the IND S/I (Dr. Maakaron) 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.

11.4 Site Monitoring

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 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.

In addition, the Clinical Trials Office (CTO) will keep a master log in OnCore of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient.

Please contact the CTO before destroying any study related records.

12 Statistical Considerations

12.1 Study Design, Objectives and Endpoints

This is a Phase I study of FT538 for the treatment of patients with relapsed/refractory CD38 expressing hematological malignancies. The primary endpoint is the maximum tolerated dose (MTD) of FT538 when given in combination with daratumumab.

The primary analysis will be intent-to-treat in that all patients receiving the 1st infusion of FT538 will be evaluable for toxicity and efficacy. Patients who discontinue therapy prior to infusion #1 will be replaced. We expect that the number of patients coming off therapy prior to infusion #1 will be minimal.

There are 5 potential dose levels defined for Phase I. The trial will be conducted with no intra-patient escalation. The starting dose will be $1x10^8$ FT538 cells with a safety dose of $5x10^7$ FT538 cells. The subsequent planned cohorts will be $3x10^8$ FT538 cells,

$1x10^9$ FT538 cells and 1.5 $x10^9$ FT538 cells (Table 1). Given that little to no toxicity is expected, the MTD will be determined using an adaptation of the continual reassessment method (CRM) (O'Quigley, 1996) starting with 1 patient cohorts.

Table 1. FT538 Dose Level and Schedule

Dose Level	Treatment Plan for FT538
-1	5×10^7 cells on Day 1, Day 8 and Day 15
1 (start)	1×10^8 cells on Day 1, Day 8 and Day 15
2	3×10^8 cells on Day 1, Day 8 and Day 15
3	1×10^9 cells on Day 1, Day 8 and Day 15
4	1.5×10^9 cells on Day 1, Day 8 and Day 15

Phase I will be conducted in two consecutive stages (non-CRM and CRM). A minimum of 28 days must separate each cohort. Within a 3 patient cohort, a minimum of 14 days must separate the 1st and 2nd patients. All patients are assessed for Dose Limiting Toxicity (DLT) as defined in the schema and Section 6.3.1.

STAGE 1 STEP 1 Fast-track design (1 patient per dose cohort)

Start at Dose Level 1 (DL1), enroll 1 patient per dose cohort separated by 28 days (DLT period) until the:

- **1st pre-defined adverse event** defined as any Grade 3 non-hematologic AE within 72 hours of a FT538 infusion
- and the patient completes the 28 day DLT period with no DLT- **Activate Stage 1 Step 2**

OR

- **1st DLT event** within 28 days after the 1st dose of FT538 as defined in the Schema and in Section 6.3.1 - **Activate Stage 2** (Stage 1 Step 2 is not used)

OR

- **10 patients are treated at the Dose Level 4** (This completes enrollment - Stage 1 Step 2 and Stage 2 are not used)
- If the first patient at dose level 4 in stage 1 step 1 completes the DLT period with no pre-defined adverse events or DLT, successive subjects may enroll without staggering.

STAGE 1 STEP 2 Expand current Dose Level and subsequent DLs to 3 patients

The cohort size increases from 1 to 3 patients with 2 additional patients added to the current cohort. A minimum of 14 days must pass between the enrollment of the 1st and the 2nd patient in 3 patient cohorts and a minimum of 28 days between dose cohorts. Continue dose escalation until:

- **1st DLT event** as defined in the Schema and Section 6.3.1 - **Activate Stage 2**

OR

- **10 patients are treated at the Dose Level 4** (This completes enrollment and Stage 2 is not used.)
- For Dose Level 4 in stage 1, step 2, the second and third patients may enroll immediately but must complete their DLT period prior to enrolling the rest. If no DLT events occur within the monitoring period, successive subjects may enroll without staggering.

Stage 2 is initiated at the 1st DLT. The study design changes to an application of the continual reassessment method (CRM) with an informative skeleton based on constrained maximum likelihood estimation (Iasonos & O'Quigley, 2012), (Iasonos & Ostrovnaya, 2011). Enrollment occurs in cohorts of three with a minimum of 14 days between the 1st and 2nd patient. Each new cohort of three patients is sequentially assigned to the most appropriate dose by the study statistician based on the updated toxicity probabilities once the 3rd patient in a cohort reaches Day 28 (end of DLT period). The goal will be to identify one of the 5 dose level strategies corresponding to the desired maximum toxicity rate of ≤25%. Given that we will have prior data once the CRM is initiated, no "skeleton" estimates are needed. The MTD will be identified by the minimum of the following criteria: (1) the total Stage 2 sample size of 25 is exhausted, (2) 10 consecutive patients are enrolled at the same dose. The function 'crm' from the R package 'dfcrm' will calculate posterior means of toxicity probabilities. Dose escalation of more than one level is not permitted with this design.

12.2 Statistical Analysis

The MTD will be determined by design. Response will be estimated with simple proportions and descriptive plots. The secondary endpoints of overall survival and progression-free survival will be estimated with Kaplan-Meier curves. Safety measures will be described with frequencies and proportions. Further descriptive statistics and plots such as boxplots, spaghetti plots and swimmer plots will be used to assess kinetics and other markers of efficacy and toxicity.

12.3 Sample Size

A maximum of 25 patients will be enrolled during Phase I with a target DLT rate of ≤25%. Based on the simulations from Table 11, this should be sufficient and safe to define the MTD. Although complete skeleton estimates will not be determined until Stage 2, Table 11 is calculated based on hypothesized values.

Table 11. Operating characteristics for Adaptive-CRM

Cells/ dose	Expected DLT, Expected SAE[1,2]			Excessive DLT, Excessive SAE		
	True Probability	Prob. of dose[3]	N[4]	True Probability	Probability of dose	N

5 x 10^7 cells (-1)	1%, 2%	0%	0	15%, 18%	55%	13
1 × 10^8 cells (1)	3%, 5%	0%	1	25%, 29%	37%	9
3 × 10^8 cells (2)	6%, 8%	1%	3	45%, 50%	7%	3
1 × 10^9 cells (3)	8%, 12%	1%	3	60%, 66%	1%	0
1.5 × 10^9 cells (4)	10%, 15%	98%	10	70%, 77%	0%	0

1. SAE's without a DLT trigger step 2 in stage 1, DLT's regardless of SAE's trigger stage 2
2. Expected/Excessive values are the hypothesized true values under the simulation
3. Probability of dose chosen as the MTD using the Adaptive-CRM design
4. The hypothesized number of patients enrolled at each dose during the trial under the assumed hypothesized "true" probabilities

Enrollment will most likely include 17 patients or it could be as high as 25 patients if DLTs are encountered early.

12.4 Monitoring Guidelines (Early Study Stopping Rules)

Stopping Rule for Excessive DLT

A stopping rule is in place during the Phase I study to stop the trial in case there are excessive DLTs as defined by updated posterior probabilities throughout the trial. At the end of the 28-day evaluation period after each cohort of patients is enrolled, new posterior probabilities will be calculated for each dose. The trial will be stopped if the posterior probability that the lowest dose is unacceptably toxic (> 25% of patients) is greater than 80%. (Zohar & Chevret, 2001)

Stopping rules also are in place independent of dose escalation. (Ivanova, 2005).

Infusion Related Reaction within 28 Days of the 1st Dose of FT538

The goal is to construct a boundary based on Grade 4 infusion related reaction such that the probability of early stopping is at most 10% if the rate is equal to 5% and our sample size is at most 25. With these stipulations, the trial will be stopped and reviewed if 2/7, 3/16 or 4 patients have events by Day 28. If the true probability of infusion related toxicity is 20%, there is an 82% chance of triggering the monitoring boundary. If the sample size is only 17 patients, the probability of triggering the monitoring boundary drops to 67%.

Aplasia at Day 42 (ANC <500) after at least 1 week of growth factor (i.e. G-CSF) with an aplastic bone marrow in the absence of leukemia (<5% cellularity)

The goal is to construct a boundary based on aplasia such that the probability of early stopping is at most 10% if the rate is equal to 5% and our sample size is at most 25. With these stipulations, the trial will be stopped and reviewed if 2/7, 3/16 or 4 patients have events by Day 42. If the true probability of aplasia is 20%, there is an 82% chance

of triggering the monitoring boundary. If the sample size is only 17 patients, the probability of triggering the monitoring boundary drops to 67%.

Early Death (Grade 5 Event) within 28 days after the last dose of FT538
Enrollment will be suspended and reviewed by the study team with follow-up notification to the FDA and IRB of the findings before enrollment is restarted for any death within 28 days after the last dose of FT538 and not attributable to disease progression. At 25 patients, if the true probability of early death is 5%, there is a 93% chance of triggering the monitoring boundary. If the sample size is only 17 patients, the probability of triggering the monitoring boundary drops to 73%.

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 – Karnofsky Performance Status Scale/Lansky Play–Performance Scale

Karnofsky Performance Status Scale Definitions Rating (%) Criteria

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly
	0	Dead

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Lansky Play-Performance Scale for Pediatric Patients (<16 years of age)	
Rating	**Description**
100	Fully active, normal
90	Minor restrictions with strenuous physical activity
80	Active, but gets tired more quickly
70	Both greater restriction of, and less time spent in, active play
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	Stuck in bed; needs help even for quiet play
20	Often sleeping; play is entirely limited to very passive activities
10	Does not play nor get out of bed
0	unresponsive

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Appendix II – New York Heart Association (NYHA) Classification

- Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
- Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
- Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20—100 m).Comfortable only at rest.
- Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Appendix III - Risks Associated with Cyclophosphamide and Fludarabine

Warnings and precautions ascribed to cyclophosphamide (CY) include:

- Myelosuppression, immunosuppression, bone marrow failure, and infections (see next section)
- Urinary tract and renal toxicity including hemorrhagic cystitis, pyelitis, ureteritis, and hematuria
  - Urinary tract obstructions must be corrected prior to receipt of CY.
- Cardiotoxicity including myocarditis, myopericarditis, pericardial effusion, arrythmias, and congestive heart failure, which may be fatal
  - Study participants should be closely monitored, especially those with risk factors for cardiotoxicity or pre-existing cardiac disease.
- Pulmonary toxicity including pneumonitis, pulmonary fibrosis, and pulmonary veno-occlusive disease leading to respiratory failure
- Secondary malignancies
- Veno-occlusive liver disease, which can be fatal
- Embryo-fetal toxicity

Adverse reactions reported most often include neutropenia, febrile neutropenia, fever, alopecia, nausea, vomiting, and diarrhea.

For the complete safety profile of CY, as well as information regarding supportive care and management of associated toxicities, refer to the current prescribing information (USPI).

Warnings and precautions ascribed to fludarabine (FLU) include:

- Severe bone marrow suppression, notably anemia, thrombocytopenia, and neutropenia (see below)
- Transfusion-associated GvHD
  - Use only irradiated blood products for transfusions.
- Severe CNS toxicity
  - Severe CNS toxicity was observed in patients treated at FLU doses of 96 mg/m2 for 5-7 days. This toxicity was observed in ≤0.2% of patients treated at FLU doses of 25 mg/m2
  - Infections
- Renal insufficiency
  - The subject's renal function should be monitored closely.
- Tumor lysis syndrome (Section 7.7)
- Embryo-fetal toxicity

Adverse reactions occurring in >30% of subjects treated with FLU include myelosuppression (neutropenia, thrombocytopenia, and anemia), fever, infection, nausea and vomiting, fatigue, anorexia, cough, and weakness.

For the complete safety profile of fludarabine, as well as information regarding supportive care and management of associated toxicities, refer to the current prescribing information (USPI).

Risks of CY/FLU when given with adoptive cell therapies:

Some adoptive cell therapies delivered with supportive medications, such as CY and FLU for conditioning, 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 for the development of cytopenias and infections is strongly recommended. Management of cytopenias and infections, including transfusion support, antimicrobial prophylaxis, and use of growth factors, should be done in accordance with standard institutional practice.

Appendix IV – European LeukemiaNet (ELN) Response Criteria in Acute Myelogenous Leukemia

The European LeukemiaNet (ELN) response criteria in acute myelogenous leukemia (AML) (Döhner 2017) are presented below.

Method of Assessment
Assessments of response in AML are performed primarily through analysis of bone marrow biopsy/aspirate and peripheral blood for enumeration of leukemic blasts. A single blood draw can be used for both hematology and disease response assessment if collected within 1 week of bone marrow biopsy with aspirate collection. Radiographic methods may be used to document extramedullary disease.

Categories of response, death due to treatment failure, and relapse are summarized in AIV-Table 1. Peripheral blood collection for tumor response assessment should be done on the same day as other tumor response assessment procedures, e.g., bone marrow biopsy/aspirate.

Testing for measurable residual disease (also known as minimal residual disease [MRD]) should be done per institutional practice. If done, the method with which MRD was tested, e.g., multiparameter flow cytometry (MFC) or molecular-based methodologies, e.g., reverse transcription polymerase chain reaction (RT-PCR), should be documented in the electronic Case Report Form (eCRF). For subjects with extramedullary disease, the same radiographic method used to evaluate extramedullary disease at baseline should be used in subsequent tumor assessments.

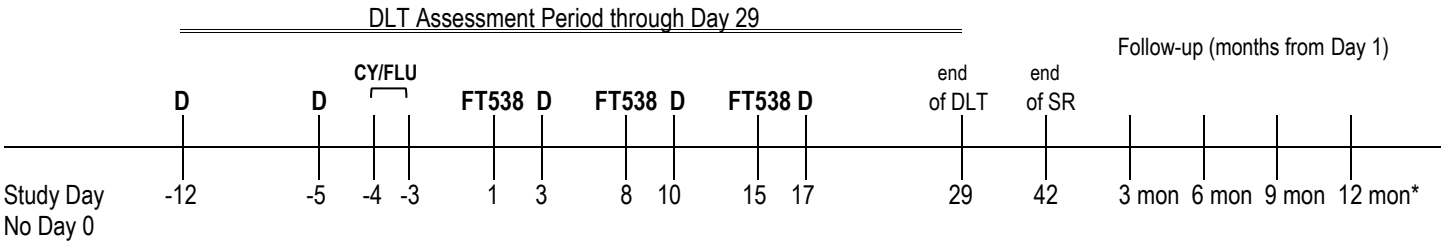
AIV-Table 1 European LeukemiaNet Response Criteria in Acute Myelogenous		
Category	Definition	Comment
Response		
Complete remission (CR) without minimal residual disease (CRMRD−)	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity for MRD by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
Complete remission (CR)	• Bone marrow blasts <5%; • Absence of circulating blasts and blasts with Auer rods; • Absence of extramedullary disease; [c] • ANC ≥1.0 × 10e9/L (1000/μL); •Platelet count ≥100 × 10e9/L (100,000/μL)	MRD+ or unknown
CR with incomplete hematologic recovery (CRi)	All CR criteria except for residual neutropenia (<1.0 × 10e9/L [1000/μL]) or thrombocytopenia (<100 × 10e9/L [100,000/μL])	
Morphologic leukemia-free state (MLFS)	• bone marrow blasts <5%; • Absence of blasts with Auer rods; • Absence of extramedullary disease; • No hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%
Partial remission (PR)	• All hematologic criteria of CR; • Decrease of bone marrow blast percentage to 5% to 25%; and • Decrease of pretreatment bone marrow blast percentage by at least 50%	
Stable disease (SD)	Absence of CRMRD–, CR, CRi, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 months
Progressive disease (PD) [a, b]	Evidence for an increase in bone marrow blast percentage and/or absolute blast counts in blood. • 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70%over at least 3 months; without at least a 100%improvement in ANC to an absolute level • (>0.5 × 10e9/L [500/ μL], and/or platelet count to >50 × 10e9/L [50,000/μL] non-transfused); or • >50% increase in peripheral blasts (WBC × %blasts) to >25 × 10e9/L (>25,000/μL) (in the absence of differentiation syndrome); [b] or • New extramedullary disease [c]	• A confirmatory marrow assessment to document blast increase may be performed after at least 4 weeks; the date of progression should then be defined as of the first observation date • "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms. In these cases, a marrow assessment, and radiographic evaluation of extramedullary disease if applicable, should be performed.
Death Due to Treatment Failure		
Death in Aplasia	• Deaths occurring ≥7 days following completion of initial treatment while cytopenic; • With an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia	
Death from indeterminate cause	• Deaths occurring before completion of therapy, or <7 days following its completion; or • Deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available	
Relapse		
Hematologic relapse (after CRMRD-, CR, CRi)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood or development of exmedullary disease	

AIV-Table 1 European LeukemiaNet Response Criteria in Acute Myelogenous		
Category	Definition	Comment
Molecular relapse (after CRMRD-)	If studied pretreatment, reoccurrence of MRD as assessed by RT–qPCR or by MFC	Test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

ANC, absolute neutrophil count; CR, complete remission; IDH, isocitrate dehydrogenase; MFC, multiparameterflow cytometry; MLFS, morphologic leukemia-free state; MRD, measurable residual disease (also known as minimal residual disease); RT-qPCR, real-time quantitative polymerase chain reaction; WBC, white blood cell.
a “Progressive disease” is a new provisional category that is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.
b Certain targeted therapies, e.g., those inhibiting mutant IDH proteins may cause a differentiation syndrome, i.e., a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.
c Radiographic evaluation of extramedullary disease per investigator discretion. The same radiographic modality used to assess extramedullary disease at baseline should be used in subsequent tumor response assessments.
Source: Döhner et al. 2017.

Appendix V: Initial Version of Study Schema, reflecting initial lymphodepletion regimen and daratumumab schedule, effective 27-Jan-2021 to 24-Nov-2022)

There is no Day 0 in this treatment plan.



D: DARZALEX FASPRO (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously (subQ) once a week for 5 doses on Day -12, Day -5, and Day +3, Day +10, Day+17

CY/FLU: Cyclophosphamide 300 mg/m^2 and fludarabine (FLU) 25 mg/m^2 administered by IV infusion on 2 consecutive days (Day -4 and Day -3)

FT538: administered at assigned dose as an IV infusion via gravity on Day 1, Day 8, and Day 15

All patients are monitored for dose limiting toxicities (DLTs) and unacceptable toxicity using early stopping rules (SRs)
Day 29 end of dose limiting toxicity (DLT) assessment (DLTs are defined on the next page and in Section 6.3.1 of the protocol)
Day 42 end monitoring for excessive toxicity (SR events are defined on the next page and in Section 6.3.2 of the protocol)

*after the 12 month visit, follow-up transfers to the long-term follow-up (LTFU) study

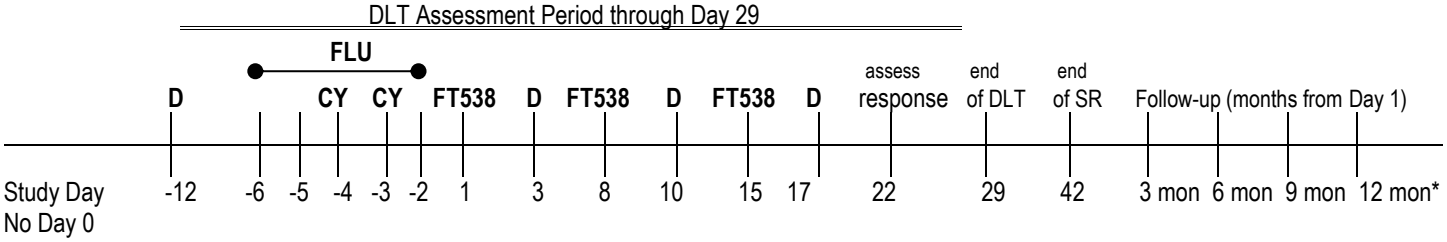
Up to 5 dose levels of FT538 will be tested (including, a DL -1, only used in event of DLT at DL 1):

Dose Level (DL) Cohort	FT538 cells/dose
-1	5×10^7
1 (start)	1×10^8
2	3×10^8
3	1×10^9
4	1.5×10^9

Each DL Cohort is separated by a minimum of 28 days (end of the DLT period). A minimum of 14 days must pass between the enrollment of the 1st and the 2nd patient in 3 patient cohorts.

Appendix VI: Second Version of Study Schema, increased lymphodepletion with initial daratumumab schedule (Amended 11/24/2022, effective 11/24/2022 through 03/20/2023)[2]

There is no Day 0 in this treatment plan.



D: DARZALEX FASPRO (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously (subQ) once a week for 5 doses on Day -12, Day -5, and Day +3, Day +10, Day+17

FLU: fludarabine (FLU) 25 mg/m^2 administered by IV infusion for 5 consecutive days, Day -6, Day -5, Day -4, Day -3, and day -2.

CY: Cyclophosphamide 60 mg/kg administered by IV infusion for 2 consecutive days, Day -4 and Day -3

FT538: administered at assigned dose as an IV infusion via gravity on Day 1, Day 8, and Day 15

All patients are monitored for dose limiting toxicities (DLTs) and unacceptable toxicity using early stopping rules (SRs)
Day 29 end of dose limiting toxicity (DLT) assessment (DLTs are defined on the next page and in Section 6.3.1 of the protocol)
Day 42 end monitoring for excessive toxicity (SR events are defined on the next page and in Section 6.3.2 of the protocol)

*after the 12 month visit, follow-up transfers to the long-term follow-up (LTFU) study

Up to 5 dose levels of FT538 will be tested (including, a DL -1, only used in event of DLT at DL 1):

Dose Level (DL) Cohort	FT538 cells/dose
-1	5 x 10^7
1 (start)	1 × 10^8
2	3 × 10^8
3	1 × 10^9
4	1.5 × 10^9

Each DL Cohort is separated by a minimum of 28 days (end of the DLT period). A minimum of 14 days must pass between the enrollment of the 1st and the 2nd patient in 3 patient cohorts.

[2] Subjects enrolled prior to 24-Nov-2022 received Cy-Flu lymphodepletion on day -4 and day -3 only. See Appendix V for previous schema.