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

Intraperitoneal FT538 with Intravenous Enoblituzumab in Recurrent Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

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University of Minnesota
Principal Investigator/IND Sponsor:
Melissa A Geller, MD
Department of Obstetrics and Gynecology
420 Delaware Street SE MMC 395
Minneapolis, MN 55455
Phone: 612 626-3111
Email: gelle005@umn.edu

Collaborators:
Jeffrey S Miller, MD*
David H McKenna, Jr., MD*
*Will not consent patients to enroll on study

Biostatistician:
Qing Cao, MS

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Revision History

Revision #	Version Date	Summary Of Changes	Consent Changes
	Mar 4 2022	Original to FDA	n/a
	May19 2022	Initial version to the CPRC: In response to FDA Clinical Information Request #1: • Increase Stage 1 Step 1 patient cohort size from 1 patient to 2, increase minimum enroll from 19 to 22 • Synopsis and Section 5.1: New inclusion criteria: o Prior treatment with bevacizumab o If BRCA positive, must have failed a prior PARP inhibitor • Section 9.2: in risks of drugs similar to enoblituzumab, clarify hormone gland problems as hypothyroidism and adrenal insufficiency Other edits and clarifications: • Expanded the definition (Italic language is new or updated wording) of the pre-defined AE as occurring in *either of the 2 patients* (previously 1 patient) and clarified Grade 3 abdominal pain *within 28 days of the 1st dose* lasting more than 48 *despite treatment with* standard analgesics or Grade 3 infusion related reaction *within 24 hours after the 1st FT538 infusion or the 1st dose of enoblituzumab and symptoms resolved to baseline within 12 hours*. • Delete pharmacodynamics of peritoneal fluid from correlative objectives as could not be performed in previous study. • Section 7.4.2 – add product administration guidelines.	yes
1	Sep 9 2022	Prior to patient enrollment: • Synopsis and Section 5.1: Clarified the intent of inclusion criterion for participants with BRCA mutations to state they must have *received* and not failed a prior PARP inhibitor.	n/a

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Key Abbreviations

Abbreviation	Definition
ABW	actual body weight
ADCC	antibody dependent cell-mediated cytotoxicity
ADL	activities of daily living
AE	adverse event
AESI	adverse events of special interest
ASTCT	American Society for Transplantation and Cellular Therapy
CAR	chimeric antigen receptor
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CNS	central nervous system
CRM	continual reassessment method
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CY/FLU	cyclophosphamide/fludarabine
DC	dose cohort
DLCO	diffusing capacity of the lungs for carbon monoxide
DLT	dose limiting toxicity
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GvHD	graft-versus-host disease
IB	Investigator's Brochure
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICE	Immune Effector Cell-Associated Encephalopathy
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IP	intraperitoneal
IRB	Institutional Review Board
IRR	Infusion related reaction
IRR/CRS	infusion related reaction/cytokine release syndrome
IV	intravenous
LTFU	long-term follow-up
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
NYHA	New York Heart Association
OS	overall survival
PARP	Poly (ADR-Ribose) Polymerase
PBMC	peripheral blood mononuclear cell
PD	progressive disease or disease progression
PFS	progression free survival
PFT	pulmonary function test
SAE	serious adverse event
SD	stable disease
SOC	standard of care
SUSAR	Serious Unexpected Suspected Adverse Reaction
TRM	treatment related mortality
ULN	upper limit of normal
USPI	United States Prescribing Information

Protocol Synopsis

Intraperitoneal FT538 with Intravenous Enoblituzumab in Recurrent Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

Study Design:

This is a single center Phase I clinical trial of FT538 administered intraperitoneally (IP) once a week for 3 consecutive weeks for the treatment of recurrent gynecologic cancers. As this is an early 1st in human study and the 1st intraperitoneal (IP) infusion of FT538, the safety of FT538 is confirmed prior to the addition of intravenous (IV) enoblituzumab. Enoblituzumab is given on Day-6 prior to the 1st dose of FT538 and every 3 weeks beginning on Day 22 until disease progression or unacceptable toxicity. A short course of outpatient lymphodepleting chemotherapy is given before the 1st dose of FT538, but after the 1st enoblituzumab infusion for patients assigned to Dose Cohort 5 or Dose Cohort 6.

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 and c) interleukin (IL)-15/IL-15 receptor alpha fusion protein. Enoblituzumab is an Fc-optimized monoclonal antibody that targets B7-H3 which is highly expressed on ovarian cancer.

This study is conducted based on the following Dose Cohorts:

Dose Cohort (DC)	Treatment Plan
-1	IP FT538 monotherapy 5 x 10^7 cells/dose on Day 1, Day 8, and Day 15
1 (start)	IP FT538 monotherapy 1 x 10^8 cells/dose on Day 1, Day 8, and Day 15
2	IP FT538 monotherapy 3 x 10^8 cells/dose on Day 1, Day 8, and Day 15
3	IP FT538 monotherapy 1 x 10^9 cells/dose on Day 1, Day 8, and Day 15
4	IP FT538 monotherapy 1.5 x 10^9 cells/dose on Day 1, Day 8, and Day 15
5	IP FT538 at the safe dose (MTD-1) from the 1st 4 dose cohorts on Day 1, Day 8, and Day 15 plus IV enoblituzumab on Day -6, Day 22, then every 3 weeks until PD
6	IP FT538 at the highest dose (MTD) from the 1st 4 dose cohorts on Day 1, Day 8, and Day 15 plus IV enoblituzumab on Day -6, Day 22, then every 3 weeks until PD

For study endpoints, follow-up continues until disease progression and then for survival only for 1 year from the 1st dose of FT538.

Enrollment Plan:

A minimum of 28 days must separate each Dose Cohort. A minimum of 14 days must separate the 1st and 2nd patient. All patients are assessed for Dose Limiting Toxicity (DLT) as defined in the Schema and in Section 7.5.

STAGE 1 STEP 1 Fast-track design (2 patients per dose cohort)

Start at Dose Cohort 1, enroll 2 patients per dose cohort separated by a minimum of 14 days until:

- The 1st occurrence of a pre-defined adverse event in either patient defined as one of the following treatment emergent events: Grade 3 abdominal pain, not attributable to the cancer, within 28 days after the 1st FT538 infusion lasting more than 48 hours despite treatment with standard analgesics or a Grade 3 infusion related reaction within 24 hours after the 1st FT538 infusion in any dose cohort or 1st enoblituzumab infusion in DC 5 or DC 6 and symptoms resolve to baseline within 12 hours.
- and both patients complete the 28 day DLT period with no DLT- **Activate Stage 1 Step 2**

OR

- **1st DLT event in either patient** within 28 days after the 1st dose of FT538 as defined in the Schema and in Section 7.5 - **Activate Stage 2** (Stage 1 Step 2 is not used)

OR

- **10 patients are treated in Dose Cohort 6** (This completes enrollment; Stage 1 Step 2 and Stage 2 are not used.)

STAGE 1 STEP 2 Expand current Dose Cohort and subsequent Dose Cohorts to 3 patients

The cohort size increases from 2 to 3 patients with 1 additional patient added to the current cohort. At least 14 days must separate the 1st and 2nd patients in a 3 patient cohort and a minimum of 28 days separate each 3 patient cohort. Continue dose escalation until:

- **1st DLT event** as defined in the Schema and Section 7.5 - **Activate Stage 2**

OR

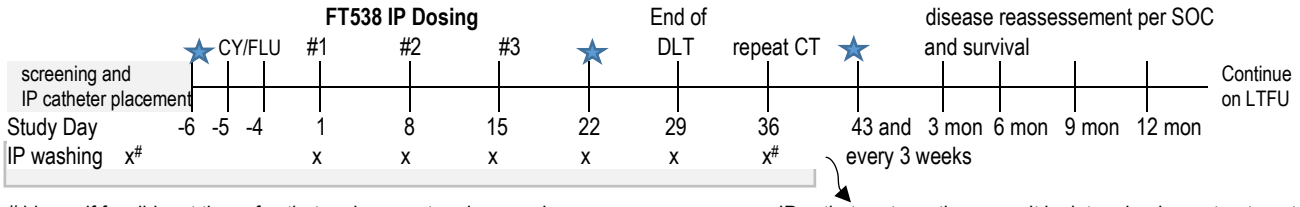
- **10 patients are treated in Dose Cohort 6** (This completes enrollment and Stage 2 is not used.)

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

The study design changes to an application of the CRM. Enrollment occurs in cohorts of 3 with a minimum of 14 days between the 1st and 2nd patient in a cohort. Each new cohort of 3 patients is sequentially assigned to the most appropriate FT538 dose level by the study statistician based on the updated toxicity probabilities once the 3rd patient in a cohort completes the 28 day DLT period. The MTD is identified by the minimum of the following criteria: (1) the total sample size of 33 is exhausted or (2) 10 consecutive patients are enrolled in the same Dose Cohort.

Investigational Product (IP):	• FT538 provided by Fate Therapeutics • Enoblituzumab provided by MacroGenics, Inc. (Cohort 5 and Cohort 6 only)
Study Agents:	Lymphodepleting chemotherapy (fludarabine and cyclophosphamide)
Long-Term Follow-Up:	The FDA recommends a 15-year safety follow-up from the 1st dose of a genetically modified cell therapy. Data collection is achieved through a separate long-term follow-up (LTFU) study. Consent to the LTFU study is done at the time of enrollment into the treatment study.
Primary Objective:	To determine the maximum tolerated dose (MTD) of FT538 monotherapy when administered via intraperitoneal (IP) catheter and in combination with intravenous (IV) enoblituzumab in patients with recurrent ovarian, fallopian tube, and primary peritoneal cancer.
Secondary Objectives:	• To characterize the toxicities associated with IP FT538 when administered as monotherapy and after IV enoblituzumab. • To estimate progression-free survival (PFS) and overall survival (OS) at 6 months and 12 months from the 1st dose of FT538. • To gain preliminary efficacy information based on RECIST 1.1 of this treatment combination.
Correlative Objectives:	Blood and ascites and/or intraperitoneal washings including: • To characterize the pharmacokinetics (PK) of FT538 monotherapy and in combination with enoblituzumab in the peritoneal fluid, peripheral blood, and tumor biopsy samples. • To assess the association of PK of FT538 monotherapy and in combination with enoblituzumab in the peritoneal fluid in this patient population with safety and anti-tumor activity. Tumor biopsies including: • To assess tumor microenvironment.
Key Inclusion Criteria:	• Recurrent epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer meeting one of the following minimal prior treatment requirement (no maximum number of prior treatments): platinum resistant: FT538 may be given as 2nd line (first salvage therapy) platinum sensitive: FT538 may be give as 3rd line therapy (second salvage therapy) • Must have received prior bevacizumab. • In the presence of a BRCA mutation, must have received a prior PARP inhibitor. • Must have measurable disease per RECIST1.1 within the abdomen and pelvis as assessed within 42 days prior to the 1st FT538 infusion. • Extra-peritoneal disease is permitted; however each lesion must be <5 cm in diameter. • Agrees to the placement of an intraperitoneal catheter before the 1st dose of study directed therapy (chemotherapy or for Cohorts 5 and 6, enoblituzumab) and remains in place through around Day 36 or the decision not to re-treat is made. • ≥ 18 years of age at time of consent signing, GOG performance status ≤ 2. • Patient weight of ≥ 50 kg due to FT538 fixed cell dosing and FT538 product pre-dosed packaging. • Adequate organ function within 14 days (28 days for cardiac and pulmonary) of study treatment start as defined in Section 5.1.7 of the protocol. • Provides written consent to the companion LTFU study. • Voluntary written consent for this study.
Key Exclusion Criteria:	• Pregnant or planning to become pregnant in the next 6 months. • Known allergy to the following FT538 components: albumin (human) or DMSO • Currently receiving or likely to require systemic immunosuppressive therapy (e.g., prednisone >5 mg daily) for any reason from Day -5 to 14 days after the last dose of FT538 (Day 29) with the exception of corticosteroids as a pre-medication per institutional standard of care – inhaled and topical steroids are permitted. • Prior enoblituzumab • Receipt of any investigational agent within 28 days prior to the first dose of FT538 (or enoblituzumab) • Known seropositive for HIV or known active Hepatitis B or C infection with detectable viral load by PCR
Enrollment Goal	Enrollment will most likely include 22 patients, or it could be as high as 33 patients if DLTs are encountered early.
Accrual Plan:	Accrual should range from 10-12 patients per year - study accrual is expected to be completed within 24-36 months.

Study Schema



biopsy if feasible, at time of catheter placement and removal

remove IP catheter at any time once it is determined no retreatment

Refer to Section 6.4 for off-study procedures if IP catheter cannot be placed by interventional radiology

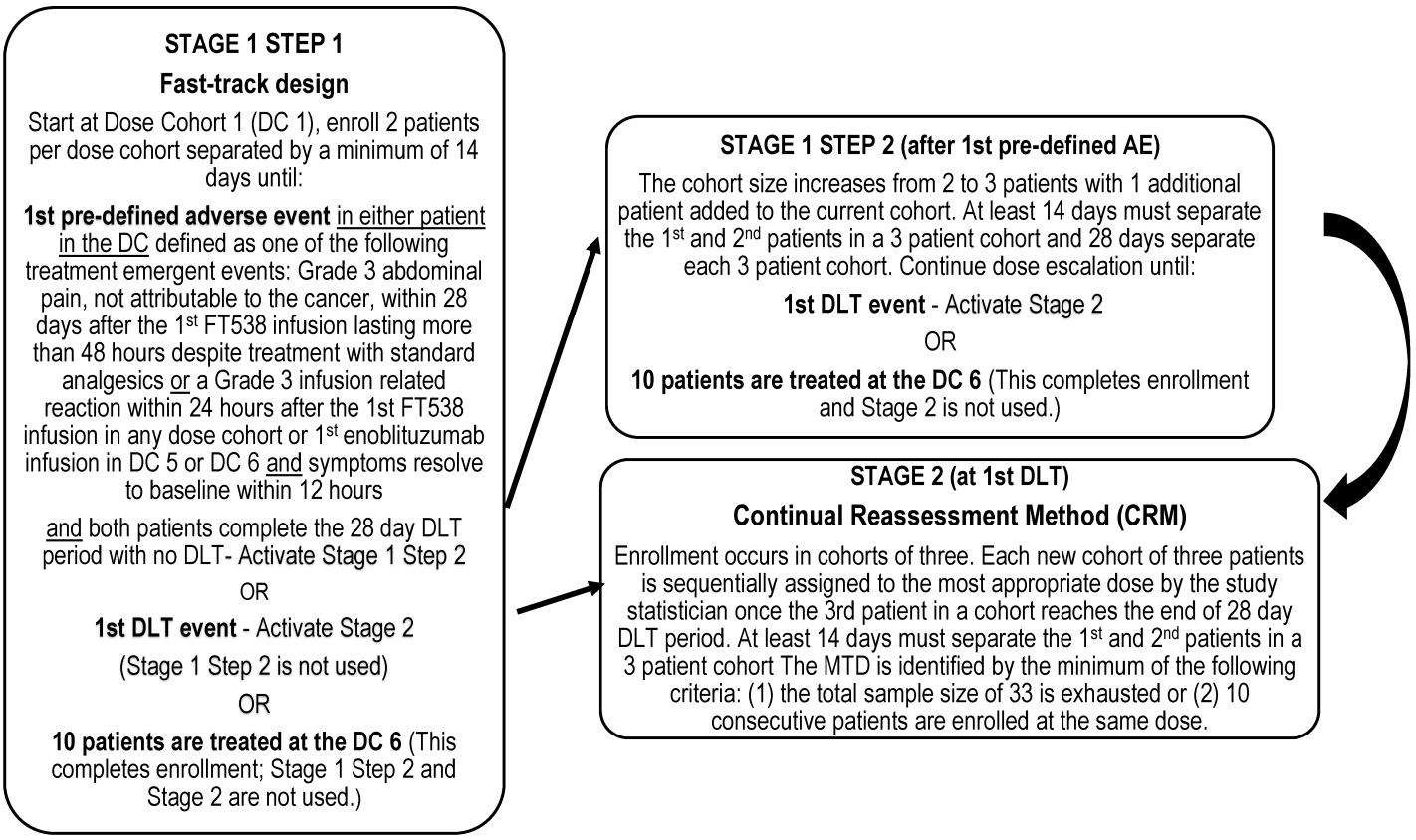
★ **Enoblituzumab** (Cohort 5 and Cohort 6 only) Enoblituzumab 15 mg/kg IV begin on Day -6 and continuing once every 3 weeks beginning on Day 22 until disease progression or unacceptable toxicity – refer to Section 7.2.1 for timing of the enoblituzumab dose on Day 22 if steroid pre-meds are needed due to an infusion reaction with the 1st enoblituzumab dose as there is a 14 day ban on corticosteroid use after the last dose of FT538

CY/FLU Lymphodepleting Chemotherapy: Fludarabine 25 mg/m^2 IV followed by CY 300 mg/m^2 IV) given on 2 consecutive days (Day -5 and Day-4)
Refer to Section 7 for allowable treatment windows.

FT538 IP at assigned dose level on Day 1, Day 8, and Day 15

Dose Cohort (DC)	FT538 Dose IP (cells per dose)
-1	IP FT538 monotherapy 5 x 10^7 cells/dose
1 (start)	IP FT538 monotherapy 1 x 10^8 cells/dose
2	IP FT538 monotherapy 3 x 10^8 cells/dose
3	IP FT538 monotherapy 1 x 10^9 cells/dose
4	IP FT538 monotherapy 1.5 x 10^9 cells/dose
5	Safe dose (MTD-1) from 1st 4 dose cohorts + IV enoblituzumab
6	Highest dose (MTD) from 1st 4 dose cohorts + IV enoblituzumab

Day 22: Cohort 5 and 6 enoblituzumab is given on Day -6, Day 22 and every 3 weeks thereafter per Section 7.2)
Day 29: Assessment at the end of the 28 day DLT period
Day 36: Disease reassessment with CT of chest/abd/pelvis – remove catheter if no retreatment or if retreatment is planned.
Follow-up for 1 year from the 1st dose of FT538: for disease response per standard of care until disease progression, and then survival only.



Dose Limiting Toxicity (DLT) is defined as any treatment emergent toxicity at least possibly related to the investigational product(s) meeting one of the following criteria based on CTCAE v5 within 28 days (within 14 days for ascites) after the 1st FT538 infusion. For Cohort 5 and 6, DLT assessment starts with enoblituzumab and continues for 28 days after 1st FT538.

- Grade 3 organ disorders (pulmonary, hepatic, renal, or neurologic) and lasting more than 72 hours
- Grade 3 abdominal pain, not attributable to cancer, lasting more than 4 consecutive days and not controlled by standard analgesics
- Grade 3 or greater ascites within 14 days after FT538 administration in patients who had no ascites or Grade 1 ascites at enrollment and is not attributable to disease progression
- Any non-hematologic Grade 4 or 5 toxicity
- Grade 4 neutrophil count decreased that persists at Day 28 despite use of growth factor support

All patients are monitored for dose limiting toxicity during the 1st 28 days after the initial FT538 infusion. The DLT period does not end until: 1) results from lab work drawn Day 29 (+3 days) does not meet a DLT and 2) a patient assessment on Day 29 (+3 days), confirms no new DLT since the last assessment or ongoing DLT events.

Monitoring for Excessive Toxicity (all patients)

Early study stopping rules also are in place independent of dose escalation for all patients. Refer to Section 14.4 for complete details:

- Excessive dose limiting toxicity (DLT) events - the trial will be stopped if the posterior probability that the lowest dose is unacceptably toxic (> 25% of patients) is greater than 80% as determined by the study statistician.
- Grade 3 or greater Infusion Related Reaction through Day 28 in association with any FT538 infusion in any Dose Cohort or in association with enoblituzumab in Dose Cohort 5 and 6.
- Early Death (Grade 5 Event) within 28 days after the last dose of FT538.

1 Objectives

1.1 Primary Objective

The primary objective of the study is to determine the maximum tolerated dose (MTD) of FT538 monotherapy when administered via intraperitoneal (IP) catheter and in combination with intravenous (IV) enoblituzumab in patients with recurrent ovarian, fallopian tube, and primary peritoneal cancer.

1.2 Secondary Objectives

Secondary objectives of this protocol are:

- To characterize the toxicities associated with IP FT538 when administered as monotherapy and after IV enoblituzumab.
- To estimate progression-free survival (PFS) and overall survival (OS) at 6 months and 12 months from the 1st dose of FT538.
- To gain preliminary efficacy information based on RECIST 1.1 of this treatment combination.

1.3 Correlative (or Exploratory) Objectives

Blood and ascites and/or intraperitoneal washings are collected for study related analysis including:

- To characterize the pharmacokinetics (PK) of FT538 monotherapy and in combination with enoblituzumab in the peritoneal fluid, peripheral blood and tumor biopsy samples.
- To assess the association of PK in the peritoneal fluid of FT538 monotherapy and in combination with enoblituzumab in patient population with safety and anti-tumor activity.

Tumor biopsies (if feasible) at the time of catheter placement and catheter removal for study related analysis including:

- To assess tumor microenvironment.

2 Background and Significance

Ovarian cancer is the most lethal gynecologic malignancy. The estimated 5-year survival is 48% for all stages of ovarian cancer, and 29% for distant disease. Notably, 59% of women with ovarian cancer present with Stage III or IV disease, the rate of recurrence is 70 to 90% for Stage III and 90 to 95% for Stage IV (SEERS). Women who recur cannot be cured with current therapies. Our long term objective is to exploit the innate immune system to treat ovarian cancer and substantially improve survival rates.

2.1 Background

Dr. Jeffrey Miller and collaborators from the University of Minnesota pioneered the development of allogeneic haplo-identical natural killer (NK) cell cancer immunotherapy beginning in the year 2000. While previous clinical trials of methods to induce autologous NK cell activity demonstrated safety, such as prolonged treatment with low-dose subcutaneous IL-2, higher doses of IV IL-2 and infusions of ex vivo IL-2 activated NK cells, these methods failed to demonstrate clinical efficacy. As the concept of "missing self" and the rules of NK cell alloreactivity emerged, interest in the use of haplo-identical NK cells to increase anti-tumor activity was established. It was believed that effector NK cells educated in haplo-identical healthy donors could induce stronger graft-versus-leukemia effects since these cells were not exposed to immunosuppressive mechanisms found in cancer patients. Additionally, it was further hypothesized that haplo-identical donors would provide a higher frequency of alloreactive NK cells (i.e., NK cells with attenuated inhibitory receptor signaling due to the major histocompatibility complex class I mismatch between the haplo-identical NK cells and the patient's tumor cells).

We established the safety and success of adoptive transfer of allogeneic NK cell products in a trial using haplotype mismatched, related-donor NK cell products (mean NK cell dose of 2 (range 1-6.2) $x10^7$ cells/kg from a single donor apheresis), followed by subcutaneous IL-2 to induce in vivo NK survival and expansion (Miller 2005). Importantly, successful expansion of the allogeneic NK cells was achieved after a lympho-depleting regimen of high dose cyclophosphamide (Cy) and fludarabine (Flu). This chemotherapy regimen, delivered prior to NK cell transfer, transiently prevents patient T cells from rejecting adoptively transferred NK cells creating an environment conducive to NK cell expansion. Complete remissions in AML correlated with in vivo NK expansion and higher proportions of circulating (and functional) NK cells. This treatment approach leads to potent anti-tumor killing. To date, we have treated over 150 patients with refractory AML and other cancers, including ovarian, with adoptively transferred NK cells (INDs 8847, 13659, and 14448) utilizing our standard platform of Cy/Flu, followed by delivery of exogenous IL-2 or IL-15 to promote in vivo NK cell activation and expansion. Although these results are an improvement over standard salvage therapy for patients with refractory leukemia (expected CR rate of 30% with NK therapy vs 10% with current SOC), they suggest that adoptive cell therapy in its current form requires additional anti-tumor activity. (Bachanova 2014)

2.2 Natural Killer (NK) Cells

2.2.1 Natural Killer Cells as Immunotherapy

Cancer immunotherapy is a rapidly evolving field that has transformed the treatment of many tumor types including solid tumors. However, despite important advances, the majority of patients will either not respond or eventually experience disease relapse. Particularly in solid tumors, the mechanisms of tumor resistance to cancer immunotherapies are diverse and include the ability of tumors to form physical and immunologic barriers to immune effector cells such as T cells and NK cells (Melero 2014). 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 kill cancer cells by multiple mechanisms including direct cytotoxicity, cytokine secretion, and antibody dependent cell-mediated cytotoxicity (ADCC):

- Direct cytotoxicity through the targeted release of perforins and granzymes. Importantly, while 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).
- 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 cytotoxic response towards 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:

- Killing of tumor cells by NK cells results in the release of tumor antigens for recognition by the adaptive immune system (Dahlberg 2015).
- NK cells upon activation 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).

2.2.2 Experience in Delivery of NK Cell Therapy

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 a single exception (Cooley 2019), allogeneic NK cell therapies have not been associated with cytokine release syndrome (CRS) or neurotoxicity, 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 acute myelogenous leukemia (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).

Most recently we have treated three patients with advanced, recurrent ovarian cancer with FT516 on a single-center, phase I clinical trial entitled “Intraperitoneal FATE FT516 and Interleukin-2 (IL-2) with Intravenous Enoblituzumab in Recurrent Ovarian, Fallopian Tube, and Primary Peritoneal Cancer”. FT516 is an allogeneic natural killer (NK) cell immunotherapy derived from a clonal human-induced pluripotent stem cell (iPSC) line, engineered to express a high affinity, non-cleavable CD16 (hnCD16) Fc receptor. The engineered features of FT516 were designed to result in increased activity against target tumor cells as monotherapy and when combined with monoclonal antibodies (mAbs) that can mediate antibody dependent cell cytotoxicity (ADCC). In Patient #3 on this clinical trial, we found by flow cytometry, that on Day 8 following IP infusion of FT516 and IL-2 IP delivery, 65% of the NK cells were HLA-A3 negative (DONOR), however by Day 15, only 1% of NK cells in IP washings were Donor cells. Based on our findings and on convincing and evolving preclinical data, we have made the decision to transition from the FT516 product to the FT538 product proposed in this protocol. Following review of the pre-clinical data, and our recent experience with our first 3 patients in the FT516 trial, we believe that making this change is the next logical step in our research. The functional modifications of FT538 include a novel high-affinity 158V, non-cleavable CD16 (hnCD16) Fc receptor, which has been modified to augment ADCC; an IL-15 receptor fusion (IL-15RF) that promotes enhanced NK cell activity; and the elimination of CD38 expression to mitigate the potential for NK cell fratricide. Together, these features are intended to augment ADCC, enhance cell persistence and prevent anti-CD38 monoclonal antibody-induced fratricide. With

the enhanced capabilities of this cell product in combination with enoblituzumab we believe we can improve upon persistence within the peritoneal cavity.

2.3 FT538

2.3.1 Development of 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 et al. 2019; Cichocki et al. 2019); b) high-affinity, non-cleavable CD16 receptor (hnCD16; Jing et al. 2015; Zhu et al. 2020); and c) interleukin (IL)-15/IL-15 receptor alpha fusion protein (IL-15RF; Rubinstein et al. 2006; Stoklasek et al. 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 IL-15RF/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 et al. 2019). In addition, NK cells with CD38 KO have been shown to be more resistant to oxidative stress and exhibit enhanced effector function (Cichocki et al. 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 (Bibeau et al. 2009; Cartron et al. 2002; Musolino et al. 2008). In addition, hnCD16 contains the genetic alteration (S179P) that prevents cleavage of CD16 by the metalloproteinase ADAM17 (Jing et al. 2015; Lajoie et al. 2014), a mechanism in the regulation and attenuation of NK-cell activity by the tumor microenvironment (Romee et al. 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 et al. 2019).

2.3.2 Summary of Clinical Data

FT538 is currently being evaluated in a Phase I study FT538-101, *A Phase I, Open-Label, Multicenter Study of FT538 as Monotherapy in Relapsed/Refractory Acute Myelogenous Leukemia and in Combination with Monoclonal Antibodies in Relapsed/Refractory Multiple Myeloma* (ClinicalTrials.gov identifier NCT04614636) in subjects with advanced hematologic malignancies on either Regimen A (acute myelogenous leukemia [AML]; monotherapy) or Regimen B (multiple myeloma; FT538 + daratumumab). As of the data cutoff date of 01 December 2021, a total of 15 patients have been treated with FT538: 13 in Regimen A and 2 in Regimen B. Nine patients remain on study (7 patients with AML in Regimen A, all of whom have completed the initial treatment cycle and are either awaiting potential retreatment with another cycle of FT538 or are in the post-treatment/long-term follow-up period; and 2 patients with multiple myeloma in Regimen B). Six patients with AML in Regimen A discontinued from the study for the following reasons: death (n=2), Primary Investigator decision (n=2), withdrawal of consent (n=1), and “other” (n=1). The 3 patients who discontinued due to death and “other” all had progressive disease.

The most common treatment emergent adverse events (TEAEs) occurring in 3 or more patients include sepsis, hypokalemia, pneumonia, nausea, vomiting, diarrhea, febrile neutropenia, hypophosphatemia, headache, and anxiety. The most common Grade ³3 TEAEs occurring in 2 or more patients include sepsis,

pneumonia, febrile neutropenia, lymphocyte count decreased, and platelet count decreased. Serious TEAEs occurring in 2 or more patients include sepsis, pneumonia, and febrile neutropenia. No DLTs or serious adverse events (SAEs) assessed as possibly or probably related to FT538 have been observed to date in any patient. No cytokine release syndrome (CRS), neurotoxicity related to FT538, or GvHD were observed. One event of Grade 3 TLS assessed as not related to FT538 was reported.

Based on protocol-defined dose-escalation rules, the FT538 dose of 1×10^8 did not exceed the maximum tolerated dose, and therefore dose escalation to the 3×10^8 dose level could proceed. Enrollment is ongoing at a dose level of 3×10^8 cells for this regimen as of 01 December 2021. To date, 3 AML subjects have been treated at a dose of 3×10^8 cells with 2 of the 3 subjects completing the DLT assessment period. One subject received all three planned doses of FT538; but did not complete the DLT assessment period due to early progressive disease and began a new anti-cancer regimen on Study Day 19. None of the 3 subjects experienced a DLT, nor were any episodes of CRS, ICANS or acute GVHD observed.

Evaluation of the multiple myeloma cohort of Regimen B (FT538 + daratumumab) is ongoing at the first dose level of 1×10^8 cells.

Overall, based on the available aggregate safety data, FT538 appears to be tolerable at the doses tested to date, up to 3×10^8 cells, without evidence of unexpected FT538-related toxicities in this preliminary evaluation. Observed toxicities are consistent with those expected with the conditioning chemotherapies in the setting of advanced relapsed/refractory disease and extensive prior therapies, with no evidence of new or unexpected toxicity signals to date. There have been no observations of acute GvHD in any of the 15 patients treated with FT538.

Refer to the FT538 Investigator's Brochure for additional details.

2.3.3 Summary of Nonclinical Data

Nonclinical data of FT538 activity was generated with FT538-R, the non-Good Manufacturing Practice (non-GMP), research-use equivalent of FT538, and include the following:

- The combination of FT538-R and ADCC-inducing mAbs, including daratumumab, resulted in enhanced anti-tumor activity as compared to mAb alone, peripheral blood NK cells alone, or FT538 alone.

- No safety concerns have been observed. A 3-month Good Laboratory Practice (GLP) toxicology study revealed no FT538-R−related serologic or histologic evidence of toxicity, and no evidence of tumorigenicity was identified. •
- Biodistribution and persistence of FT538-R cells in immunodeficient NOD-SCID-IL2rγnull (NSG) mice was evaluated following three intravenous (IV) injections at 3 × 106 cells/mouse or 1.2 × 107 cells/mouse administered 7 days apart on day of study 1, day of study 8, and day of study 15. The data demonstrate that FT538-R is detected in most tissues and that their persistence generally decreases over time to a level approaching or below the lower limit of detection by day of study 67.

Additional information on nonclinical studies with FT538 is provided in the FT538 Investigator's Brochure.

2.4 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)

2.5 Enoblituzumab

MGA271 (enoblituzumab, also known as RES242) is a humanized immunoglobulin (Ig) G1/kappa monoclonal antibody (mAb) that binds B7 homolog 3 (B7-H3), also referred to as CD276, a member of the B7 family of ligands that bind to receptors on lymphocytes and regulate immune responses. This agent is being developed by MacroGenics, Inc. B7-H3 is overexpressed on a number of tumor types and the primary mechanism of action for MGA271 is thought to be via antibody-dependent cellular cytotoxicity (ADCC). MGA271 comprises an engineered human IgG1 fragment crystallizable (Fc) domain that imparts increased affinity for the human activating Fc-gamma receptor (FcγR) IIIA (CD16A) and decreased affinity for the human inhibitory FcγRIIB (CD32B). (Enoblituzumab IB).

3 Study Rationale

3.1 The Use of Intraperitoneal Administration in Gynecologic Cancers

Ovarian, primary peritoneal and fallopian tube cancers are diseases that spread locally within the peritoneal cavity. Ovarian cancer is an intraperitoneal disease, rarely metastasizing beyond the abdominal cavity, so the goal is to deliver therapy directly to the tumor site to potentially maximize efficacy. It is for this reason and based on our preclinical data, which demonstrated better anti-tumor effects with IP delivery than systemic delivery, that we have elected to deliver the FT538 within the peritoneal cavity. (Geller 2013, Uppendahl 2019) I

3.2 Rationale for Using FT538 IP Dosing

Based on our published in vivo mouse data (Hermanson 2016) our current platform for NK cell therapy in ovarian cancer delivers NK cells IP as we have seen significant inhibition of ovarian cancer growth using this delivery. As ovarian cancer is an intraperitoneal disease, rarely metastasizing beyond the abdominal cavity, therapy delivered directly to the tumor site makes intuitive sense. Recent studies conducted by our collaborators defined the lymphocyte population within the peritoneal fluid (PF) of women with high-grade serous ovarian cancer (Figure 1). They found that women with ovarian cancer had a significantly lower percentage of NK cells in the PF compared to women with benign disease. Importantly, the ovarian cancer patients with lower number of NK cells had significantly lower survival.

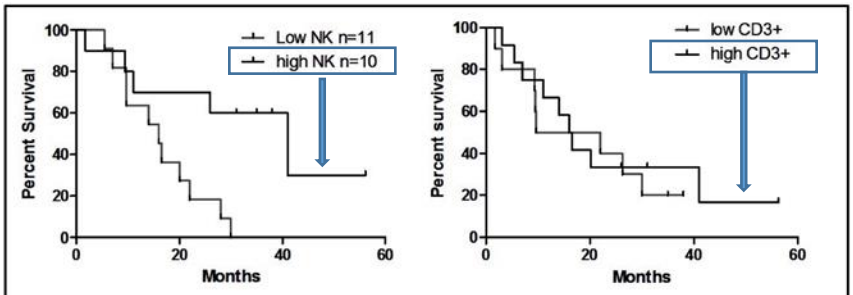


Figure 1: Kaplan Meier curve of the low NK group (<median) vs. patients with a high NK cell count in peritoneal fluid ((p<0.01). CD3 counts do not predict differences in survival. Data kindly provided by Dr. Harry Dolstra from the Radboud Institute for Molecular Life Sciences (RIMLS) at Radhoud University Medical Center.

This data provides the rationale for delivering the FT538 product directly within the peritoneal cavity. In addition, we recently completed a clinical trial where we developed a 7-day culture process using a GSK3 inhibitor and IL-15 to manufacture modulated adaptive NK cells (FATE-NK100) from CMV^+ haploidentical donors for adoptive transfer. The phase I Apollo trial tested the maximum tolerated dose/maximum feasible dose (MTD/MFD) of FATE-NK100 administered intraperitoneally (IP) to treat platinum-sensitive or -resistant recurrent ovarian, fallopian tube, and primary peritoneal cancer. FATE-NK100 via IP port

was tested using 3 dose cohorts ([DC]; 1 × 10^7 cells/kg; >1 × 10^7 cells/kg to ≤3 × 10^7 cells/kg; or >3 × 10^7 to ≤10 × 10^7 cells/kg) after lympho-conditioning with fludarabine 25 mg/m^2 IV and cyclophosphamide 300 mg/m^2 IV on days −6 and −5. After FATE-NK100 infusion on day 0, rhIL-2 at 6 million IU was given IP 3 times a week for 6 doses for in vivo NK activation. Nine patients were treated with no dose-limiting toxicities (DLTs). Retreatment based on clinical benefit was performed on 3 patients (33%), 2 following stable disease (DC 2) and 1 with partial remission (48% tumor reduction, DC 3). We found that the allogeneic product cells persist and have enhanced function compared to patient NK cells for up to 21 days, even after retreatment (our unpublished data).

We anticipate that the novel FT538 cell product will overcome the limitations of our current NK cell product, specifically by displaying better activity associated with longer survival after infusion into the peritoneal cavity. We have data showing that within the peritoneal microenvironment, the surface expression of CD16a on NK cells is significantly decreased presumed from ADAM17 mediated cleavage. This is one possible reason for decreased NK cell cytotoxicity in ovarian cancer that can be overcome with the use of the non-cleavable FT516 cell product. CD16a cell surface levels are tightly regulated by ADAM17 (Wu 2019, Romee 2013, Wang Y 2013, Jing 2015). We were the first to report that ADAM17 mediates this process by cleaving CD16a in a *cis* manner at a specific location proximal to the cell membrane. (Jing 2015) Though this is a normal process of immune homeostasis, it has been reported that NK cells in the tumor tissues of ovarian cancer patients have significantly reduced levels of CD16a (Figure 2) and impaired anti-tumor effector functions (Lai 1996, Patankar 2005, Belisle 2007, Felices 2017).

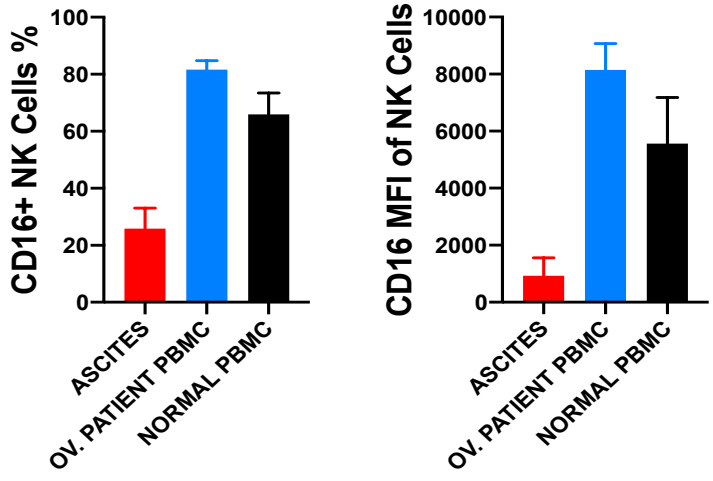


Figure 2. Percentage of CD16+ NK cells are significantly reduced in the peritoneal cavity compared to NK cells in the peripheral blood of ovarian cancer patients and in healthy patients.

3.3 Rationale for Lymphodepleting Conditioning

The purpose of conditioning prior to the administration of FT538 is to create an immune environment amenable to FT538 persistence and expansion. This is accomplished by promoting homeostatic proliferation of FT538 as well as eliminating regulatory immune cells and other competing elements of the immune system that compete for homeostatic cytokines (Klebanoff 2005). Conditioning with CY and FLU has been established with CD19 CAR T-cell therapies (Kymriah® USPI; Yescarta® USPI) and was shown to improve CAR-T expansion and persistence associated with clinical benefit (Turtle et. al. 2016). The doses and schedules of CY and FLU conditioning used in this study are identical to those administered as conditioning prior to infusion of axicabtagene ciloleucel (Yescarta USPI).

In addition to the generation of "immunologic space" to support FT538, reasons for administering lymphodepleting chemotherapy prior to the first IP dose of FT538 include:

1) Cyclophosphamide is used as a standard chemotherapy agent in the treatment of recurrent ovarian cancer (Chura 2007) and
2) We know that immunosuppression dominates the IP cavity in women with ovarian cancer (Lukesova 2015, Felices 2017). Additionally, we have data showing that the IP tumor microenvironment is highly suppressive and causes significant downregulation of CD16 (the low-affinity Fc receptor utilized by NK cells to mediate ADCC). We believe that the proposed low dose lymphodepleting regimen is still necessary to enhance FT538 anti-tumor activity.

3.4 Rationale for Retreatment with FT538

A second course of FT538 may be offered to those who experience clinical benefit at the 1st disease reassessment around Day 36. Clinical benefit is defined as stable disease or better without a decrease performance status from baseline. Advanced ovarian, primary peritoneal and fallopian tube cancers cannot be cured with current available therapies therefore, if the patient has achieved stable disease (SD) or better, it is reasonable to offer retreatment with FT538.

3.5 Rationale for Using Enoblituzumab

Clinical experience and trials have not identified an effective cancer antibody for ovarian cancer compared to others solid tumors responding to HER2 and EGFR targeted antibodies. Enoblituzumab is an Fc optimized humanized IgG1 monoclonal antibody that binds to B7-H3 (CD276). B7-H3 is widely expressed by a number of different tumor types, including a majority of ovarian cancers and

ovarian cancer stroma (MacGregor 2019), and may play a key role in regulating the immune response.

The rationale for instituting enoblituzumab into this trial is based on preclinical data showing that B7H3 expression is prevalent in the majority of ovarian cancers. Additionally, in a study by Zang and colleagues (Zang X 2010); B7-H3 was found to be expressed on 78% of the endothelium of tumor-associated vasculature from patients with Stage III and IV ovarian cancer. This suggests that targeting B7-H3 in advanced ovarian cancer may serve to target both tumor cells and cells critical for the generation and support of the tumor microenvironment. 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) mediated by NK cells. Enoblituzumab is a humanized immunoglobulin (Ig) G1/kappa monoclonal antibody (mAb) that when combined with FT538 is designed to enhance ADCC as well as direct NK-mediated cytotoxicity to B7-H3 expressing cells. The combination of FT538 and enoblituzumab has stronger mechanistic rationale which is why we have selected this combination.

4 Study Design

This is a single center Phase I clinical trial of FT538 administered intraperitoneally (IP) once a week for 3 consecutive weeks for the treatment of recurrent gynecologic cancers. As this is an early first in human study and the first intraperitoneal infusion of FT538, the safety of FT538 is confirmed prior to introducing enoblituzumab in combination with FT538. Once a safe does of FT538 is identified, enoblituzumab is added as an intravenous infusion on Day -6 and every 3 weeks beginning on Day 22 (1 week after the last dose of FT538) until disease progression or unacceptable side effects. A short course of outpatient lymphodepleting chemotherapy is given prior to the first dose of 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; b) high-affinity, non-cleavable CD16 receptor and c) interleukin (IL)-15/IL-15 receptor alpha fusion protein. Enoblituzumab is an Fc-optimized monoclonal antibody that targets B7-H3 which is highly expressed on ovarian cancer.

This study is conducted based on the following Dose Cohorts:

Dose Cohort (DC)	Treatment Plan
-1	IP FT538 monotherapy 5 x 10^7 cells/dose on Day 1, Day 8, and Day 15
1 (start)	IP FT538 monotherapy 1 x 10^8 cells/dose on Day 1, Day 8, and Day 15
2	IP FT538 monotherapy 3 x 10^8 cells/dose on Day 1, Day 8, and Day 15
3	IP FT538 monotherapy 1 x 10^9 cells/dose on Day 1, Day 8, and Day 15
4	IP FT538 monotherapy 1.5 x 10^9 cells/dose on Day 1, Day 8, and Day 15
5	IP FT538 at the safe dose (MTD-1) from the 1st 4 dose cohorts on Day 1, Day 8, and Day 15 plus IV enoblituzumab on Day -6, Day 22, then every 3 weeks until disease progression
6	IP FT538 at the highest dose (MTD) from the 1st 4 dose cohorts on Day 1, Day 8, and Day 15 plus IV enoblituzumab on Day -6, Day 22, then every 3 weeks until disease progression

A minimum of 28 days must separate each Dose Cohort. Within a Dose Cohort, a minimum of 14 days must separate the 1st and 2nd patient. All patients are assessed for Dose Limiting Toxicity (DLT) as defined in the Schema and in Section 7.5.

STAGE 1 STEP 1 Fast-track design (2 patients per Dose Cohort)

Start at Dose Cohort 1 (DC 1), enroll 2 patients per dose cohort separated by a minimum of 14 days until the:

- **The 1st occurrence of a pre-defined adverse event in either patient in a DC** defined as one of the following treatment emergent events:
  - Grade 3 abdominal pain, not attributable to the cancer, within 28 days after the 1st FT538 infusion lasting more than 48 hours despite treatment with standard analgesics

  or

  - Grade 3 infusion related reaction within 24 hours after the 1st FT538 infusion in any Dose Cohort or 1st enoblituzumab infusion in DC 5 or DC 6 and symptoms resolve to baseline within 12 hours
- and both patients complete 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 7.5 - **Activate Stage 2** (Stage 1 Step 2 is not used)

OR

- **10 patients are treated at the Dose Cohort 6** (This completes enrollment - Stage 1 Step 2 and Stage 2 are not used)

STAGE 1 STEP 2 Expand current Dose Cohort and subsequent DCs to 3 patients

The cohort size increases from 2 to 3 patients with 1 additional patient added to the current dose cohort. At least 14 days must and a minimum of 28 days separate each 3 patient cohort. Continue dose escalation until:

- **1st DLT event** as defined in the Schema and Section 7.5 - **Activate Stage 2**

OR

- **10 patients are treated at the Dose Cohort 6** (This completes enrollment; Stage 2 is not used.)

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

The study design changes to an application of the continual reassessment method (CRM). Enrollment occurs in cohorts of three with a minimum of 14 days between the 1st and 2nd patient in a cohort. Each new cohort of three patients are sequentially assigned to the most appropriate dose by the study statistician based on the updated toxicity probabilities once the 3rd patient in a cohort completes the 28 day DLT period. The maximum tolerated dose (MTD) will be identified by the minimum of the following criteria: (1) the total sample size of 33 is exhausted or (2) 10 consecutive patients are enrolled in the same Dose Cohort.

If a patient experiences clinical benefit (defined as stable disease or better and no decline in baseline performance status) after the initial treatment course, they may be offered the opportunity of retreatment using the same FT538 Dose Cohort. Refer to Section 5.3 and Section 7.8 for additional details.

For study endpoints, follow-up continues for disease response per standard of care until disease progression, and then for survival only for 1 year after the 1st dose of FT538.

After 1 year, follow-up continues on the long-term follow-up (LTFU) study to adhere to FDA's recommended 15 year follow-up after treatment with a genetically modified cell therapy. A separate consent is required for the LTFU study.

5 Patient Selection

Study entry is open to persons regardless of race or ethnic background. While there will be every effort to seek out and include minority patients, the patient population is expected to be no different than that of other gynecological cancer studies at the University of Minnesota.

A potential participant must meet all of the inclusion and none of the exclusion criteria to be considered eligible for study participation.

5.1 Inclusion Criteria

5.1.1 Recurrent epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer meeting one of the following minimal prior treatment requirements (no limit to the maximum number of prior treatments).

- Platinum Resistant: may receive FT538 as 2nd line (as 1st salvage therapy). Platinum resistant is defined as disease that has responded to initial chemotherapy but demonstrates recurrence within a relatively short period of time (< 6 months) following the completion of treatment.
- Platinum Sensitive: may receive FT538 as 3rd line therapy (as 2nd salvage therapy). Platinum sensitive is defined as the recurrence of active disease in a patient who has achieved a documented response to initial platinum-based treatment and has been off therapy for an extended period of time (≥ 6 months).

5.1.2 Must have received prior bevacizumab.

5.1.3 In the presence of a BRCA mutation, must have received a prior PARP inhibitor.

5.1.4 Measurable disease per Response Evaluation Criteria in Solid Tumors v1.1 (RECIST - refer to Appendix II) within the abdomen and pelvis assessed within 42 days of the 1st FT538 infusion. Extra-peritoneal disease is permitted; however each lesion must be < 5 cm at the largest diameter.

5.1.5 At least 18 years of age at the time of consent.

5.1.6 GOG Performance Status 0, 1, or 2 (refer to Appendix I).

5.1.7 Adequate organ function within 14 days (28 days for pulmonary and cardiac) of study treatment (CY/Flu or enoblituzumab) start defined as the following:

- Hematologic: platelets ≥ 75,000 x 10^9/L; absolute neutrophil count (ANC) ≥ 1000 x 10^9/L, unsupported by G-CSF or granulocytes
- Creatinine: Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73m^2 per current institutional calculation formula

- Hepatic: AST and ALT ≤ 3 x upper limit of institutional normal
- Pulmonary Function: Oxygen saturation ≥ 90% on room air; PFTs are performed only if known history or as medically indicated – if done, must have pulmonary function >50% corrected DLCO and FEV1.
- Cardiac Function: LVEF ≥ 40% by echocardiography, MUGA, or cardiac MRI; no clinically significant cardiovascular disease including any of the following: stroke or myocardial infarction within 6 months prior to first study treatment; unstable angina or congestive heart failure of New York Heart Association (NYHA) Grade 2 or higher (Appendix I).

5.1.8 Agrees to the placement of an intraperitoneal catheter before the 1st dose of study directed drug (chemotherapy or enoblituzumab for Cohort 5 and 6) and remains in place through Day 36 or longer if retreatment is planned. Refer to Section 6.4 if catheter cannot be successfully placed.

5.1.9 Agrees to undergo a tumor biopsy if feasible at the time the catheter is placed and removed – Accessible tumor for biopsy is not required for eligibility.

5.1.10 If history of brain metastases must be stable for at least 3 months after treatment – A brain CT scan or MRI is only be required in patients with known brain metastases at the time of enrollment or in those with clinical signs or symptoms suggestive of brain metastases.

5.1.11 Must agree to and sign the consent for the companion Long-Term Follow-Up study (CPRC# 2021LS077) to fulfill the FDA recommended 15 years of follow-up for a genetically modified cell product.

5.1.12 Voluntary written consent prior to the performance of any research related procedures.

5.2 Exclusion Criteria

5.2.1 Pregnant or breastfeeding or planning on becoming pregnant in the next 6 months. If of childbearing potential (have a uterus and ovaries) and engaged in heterosexual intercourse, must have a negative pregnancy test (serum or urine) within 14 days before the 1st CY/Flu or, enoblituzumab, if applicable. Patient must agree to use highly effective method of birth control from the screening visit until at least 12 months after the final dose of CY, at least 4 months after the final dose of FT538, or at least 3 months after the final dose of enoblituzumab, whichever is longer.

5.2.2 Currently receiving or likely to require systemic immunosuppressive therapy (e.g., prednisone >5 mg daily) for any reason from Day -5 to 14 days after the last FT538 infusion) with the exception of corticosteroids as a pre-medication per institutional standard of care – topical and inhaled steroids are permitted.

5.2.3 Active autoimmune disease requiring systemic immunosuppressive therapy.

5.2.4 History of severe asthma and currently on chronic systemic medications.

5.2.5 Uncontrolled bacterial, fungal or viral infections with progression of clinical symptoms despite therapy.

5.2.6 Receipt of any biological therapy, chemotherapy, or radiation therapy (except palliative RT), within 2 weeks prior to the first dose of FT538 (or enoblituzumab for Dose Cohorts 5 and 6) or five half-lives, whichever is shorter; or any investigational agent within 28 days prior to the first dose of FT538 (or enoblituzumab for Dose Cohorts 5 and 6).

5.2.7 Live vaccine within 6 weeks prior to start of lympho-conditioning.

5.2.8 Known allergy to the following FT538 components: albumin (human) or dimethyl sulfoxide (DMSO).

5.2.9 Prior enoblituzumab.

5.2.10 Non-malignant CNS disease such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease or receipt of medications for these conditions in the 2-year period leading up to study enrollment. (Refer to Section 5.1.8 regarding history of brain metastases.)

5.2.11 Known history of HIV positivity or active hepatitis C or B - chronic asymptomatic viral hepatitis is allowed.

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

5.2.13 Any medical condition or clinical laboratory abnormality that, per investigator judgement, precludes safe participation in and completion of the study or that could affect compliance with protocol conduct or interpretation of results.

5.3 Retreatment Criteria

A 2nd course of FT538 at the patient's original Dose Cohort assignment may be considered for participants meeting the following criteria:

5.3.1 Achieved clinical benefit from the 1st treatment course (stable disease, PR or CR based on RECIST) when comparing baseline CT scan and the CT scan performed around Day 36.

5.3.2 A functioning IP catheter.

5.3.3 No unacceptable toxicity (experienced toxicity that met the definition of a DLT and/or toxicity that caused a dose to be skipped during the first course of FT538).

5.3.4 All acute treatment related adverse events have resolved to ≤ Grade 1 or baseline, whichever is higher.

5.3.5 No decline in GOG performance status from baseline as recorded at the Day 36 visit assessment.

5.3.6 Continues to meet laboratory requirements found in Section 5.1.7.

5.3.7 If receiving enoblituzumab, able to align retreatment to the third enoblituzumab infusion (receive lymphodepleting chemotherapy within the week after enoblituzumab infusion).

5.3.8 Voluntary written consent using the retreatment consent (CPRC# 2021LS103R) prior to any retreatment activities.

6 Patient Screening and Study Enrollment

Written consent must be obtained before the performance of any research related tests or procedures, although the results of routine tests and procedures (i.e. CT scan of the chest, abdomen and pelvis) performed prior to consent may be used to determine eligibility if within the study permitted timeframe.

6.1 Consent and Study Screening Registration

Any patient who is consented is to be registered in OnCore by the 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 inclusion/exclusion criteria or eligible, but changes mind about participation), the patient's record is updated in OnCore as a screen failure and reason for exclusion recorded.

6.2 Patient Enrollment and Cohort Assignment

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 assigned to the currently enrolling cohort once eligibility is confirmed and a "treatment slot" is available.

6.3 Optional 2nd Treatment Course with FT538 (Retreatment)

After confirmation of eligibility in Section 5.3 and signing of the retreatment consent, the patient is enrolled to the retreatment study (2021LS103R) in OnCore releasing a new study calendar. Retreatment has no effect on the primary and secondary analysis; however, adverse events are documented and reported per Section 11.

6.4 Inability to Begin Study Treatment

If a patient is registered to the study and is later found not able to begin study treatment (i.e. inability to successfully place the intraperitoneal catheter, change in medical status, etc.), the patient is taken off of the study and treated at the physician's discretion. The study staff will update OnCore with the patient's non-treatment status. The reason for off study must be clearly indicated in OnCore. The patient is replaced to complete enrollment.

If a patient does not receive FT538, they also should be withdrawn from the LTFU study (CPRC #2021LS077).

7 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 any concomitant medications not otherwise described as cautionary or prohibited therapy (refer to Section 7.7) or treatment deemed necessary to provide adequate supportive care. Supportive care may include anti-microbial prophylaxis, analgesics, transfusions, growth factors, etc. Only irradiated blood products should be used to minimize the risk of transfusion-associated GvHD.

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. If receiving enoblituzumab, at least 1 day must separate the dose of enoblituzumab and the start of the lymphodepletion chemotherapy. The 1st dose of FT538 may be delayed for up to 7 days after the last dose of fludarabine in the event FT538 cannot be given as planned. Day 1 is the day of the 1st FT538 infusion. There is no Day 0.

7.1 Peritoneal Port/Intraperitoneal Catheter Placement (Day – 6 or earlier*)*

Successful placement of the IP catheter/peritoneal port is required before proceeding with the lymphodepleting chemotherapy (or the 1st dose of enoblituzumab, if applicable). If an IP catheter cannot be placed, the patient will be taken off study per Section 6.4.

The peritoneal site where the catheter is to penetrate the peritoneum is identified under direct vision by Interventional Radiology. It is important to enter the peritoneal cavity under direct vision because a previous staging laparotomy for ovarian cancer is likely to have resulted in adhesion formation, particularly between the bowel and anterior abdominal wall. The catheter insertion site through the peritoneum must be separate from other incisions.

The intraperitoneal catheter to be used in the proposed clinical study is PLEURX PERITONEAL CATHETER KIT AND PLEURX DRAINAGE KITS, which is manufactured by Becton Dickinson in Franklin Lakes, NJ. The catheter is Device Class 2 and is 510K-clearedK051711.

There is a risk for spread of cancer cells that are located within the peritoneum to surrounding tissues such as the abdominal wall. This risk is associated with the penetration of the abdominal cavity during the IP catheter placement as it exposes new surfaces for the cancer cells to attach. Implantation of malignant cells within surgical incisions and along biopsy needle and drainage catheter tracts is a recognized mechanism for the dissemination of cancer. In one review published of 255 patients with epithelial ovarian carcinoma, Dauplat et al. (Dauplat, et al. 1987) included nine cases (3.5%) with skin metastases, one of which occurred at the site of a catheter used for intraperitoneal chemotherapy. Kohler et al. (Kohler, et al. 1991) described two patients who were treated with intraperitoneal administration and subsequently developed abdominal wall metastases. In one case the lesions were at the site of previous surgical incisions. In the other, metastasis occurred at the former site of the peritoneal access catheter which had been removed after therapy 2.5 years earlier. Implantation metastases is a potential hazard of all invasive procedures in the case of malignancy. Although thought to be a rare event, placement of a peritoneal access catheter in ovarian cancer may be a risk for seeding tumor cells.

The baseline research related peritoneal cell collection (ascites or intraperitoneal washing) and a tumor biopsy, if feasible, will be done at placement. Refer to Section 10.2.1 and Section 10.2.2.

The catheter will remain in place until approximately Day 36 for peritoneal cell collection and biopsy unless progression is confirmed earlier or there are issues related to the functioning or safety of the catheter (i.e. infection, plugged up, etc.). If the patient agrees to and qualifies for retreatment, the IP catheter remains in place until approximately retreatment Day 29 (rDay 29).

7.2 Enoblituzumab (Day -6 then Day 22 and every 3 weeks thereafter) - Cohort 5 and 6 only

Treatment may be administered in the outpatient setting or as an inpatient.

Enoblituzumab 15 mg/kg is given as an intravenous infusion over 120 minutes (±15 minutes) using a commercially available pump. A sterile, non-pyrogenic, low-protein binding polyethersulfone (PES) 0.2 micron in-line filter administration set must be used for IV administration of enoblituzumab.

The full, calculated dose will be administered based on the patient's actual weight at baseline; a significant (≥10%) change in body weight from baseline should prompt recalculation of the dose. For patients with a body mass index (BMI) ≥30 kg/m2, the enoblituzumab dose will be calculated using ideal body weight (IBW).

There are no other enoblituzumab dose modifications; however, reduction in the infusion rate is permissible if the patient has experienced an infusion-related reaction

The 1st dose of enoblituzumab is given Day -6 with some flexibility as provided in the Section 7 introduction.

Subsequent doses of enoblituzumab are given every 3 weeks (±2 days) starting on Day 22 using the 1st dose of FT538 as Day 1. Refer to Section 7.2.1 regarding corticosteroid use relative to FT538 administration which may affect the Day 22. Enoblituzumab may continue until disease progression, unacceptable side effects, patient refusal or non-compliance, or felt to no longer be of benefit to the patient by the treating investigator.

If a patient is eligible for retreatment per Section 6.3, the 3rd dose of enoblituzumab (around Day 43) ideally serves as the anchor for the CY/FLU and FT-538 administration.

7.2.1 Enoblituzumab Pre-Medications and Prophylaxis Guidelines

Required prior to the first infusion of enoblituzumab:

- Acetaminophen 650-1000 mg orally (PO) or ibuprofen 400 mg PO, or equivalent
- Diphenhydramine 50 mg PO or IV or equivalent H1 antagonist
- Ranitidine 300 mg PO or IV or equivalent H2 antagonist
- Dexamethasone 10-20 mg IV

No pre-infusion prophylactic steroids are required for subsequent infusions. Non-steroidal pre-medications may be administered prior to the subsequent infusion, if warranted.

If the patient experiences a ≥ Grade 1 infusion related reaction with the first infusion refer to the recommended pre-medications found in the Infusion Related Reaction in Section 7.2.2. If a patient requires corticosteroid pre-medication for subsequent doses, the Day 22 dose must be delayed until Day 29 (or 14 days after the final dose of FT538). Beyond Day 29, steroid use is permitted as a pre-medication; however, if the patient qualifies for retreatment, the same 14 day rule for corticosteroid use applies. Changes to the enoblituzumab schedule are not a protocol deviation.

Antiemetic therapy including but not limited to neurokinin 1 (NK1) receptor antagonists, serotonin (5HT3) receptor antagonists, benzodiazepines, antihistamines, cannabinoids, cholinergic antagonists and dopamine receptor antagonists may be administered according to good clinical practice and local guidelines.

7.2.2 Monitoring During the Enoblituzumab Infusion Period

To date, the most important safety risk that has been identified with enoblituzumab is infusion-related reactions (IRR), including cytokine release syndrome (CRS) due to the release of small proteins (cytokines) from the cells. IRRs are generally temporary effects due to a drug that may occur during or shortly after infusion of the drug. Signs and symptoms of an infusion-related reaction may include fever, chills, nausea, vomiting, headache, muscle stiffness, rash, itching, low blood pressure, and difficulty breathing. IRRs can be life threatening and, in rare cases, may cause death.

Obtain vital signs (temperature, blood pressure, respiration and pulse) upon arrival, within 15 minutes prior to start of the enoblituzumab, every 15 minutes (± 5 minutes for the first hour of the infusion, every 30 minutes (±5 minutes) thereafter until infusion end, upon discontinuing the infusion, and before the patient is discharged from the clinic.

7.2.3 Management of Enoblituzumab Infusion Related Reactions

Refer to Section 9 for a list of the most common side effects associated with enoblituzumab.

Grade 3 or greater infusion related reactions are reportable as a DLT (the DLT period for Dose Cohorts 5 and 6 begins with the 1st dose of enoblituzumab through 28 days after the 1st FT538 infusion), adverse events of special interest (AESI) and/or SAEs, as applicable per Section 11.2. In the event, Cohort 5 or 6 is reached while enrollment is still in Stage 1 Step 1, a Grade 3 infusion reaction is pre-defined adverse event that triggers movement to either Stage 1 Step 2 or Stage 2 as detailed in the study design.

The following are treatment guidelines (which may be modified as needed by the Investigator according to the best practices of medicine) for infusion reactions:

Grade 1 Infusion Related Reaction:

- Slow the infusion rate by 50%.
- Monitor the patient for worsening of condition.
- Continue rate at 50% reduction and increase dose rate to the original rate by doubling the infusion rate after 30 minutes, as tolerated to the initial rate. Consideration can be given to beginning subsequent infusions at 50% rate and increasing as tolerated.
- The following prophylactic pre-infusion medications are recommended prior to future infusions of enoblituzumab for patients who experience Grade 1 infusion reactions (restrictions apply to the Day 43 infusion if FT538 retreatment is planned):
  - Diphenhydramine 25 to 50 mg (or equivalent) PO/IV.
  - Acetaminophen 650 mg PO and/or ibuprofen 400 mg PO, or equivalent, at least 30 minutes before additional enoblituzumab infusions.
  - Ranitidine 300 mg PO or 50 mg IV or equivalent H2 antagonist before additional enoblituzumab infusions.

Grade 2 Infusion Related Reaction:

- Stop the enoblituzumab infusion.
  - Administer diphenhydramine hydrochloride 25 to 50 mg IV.
  - Acetaminophen 650 mg PO or ibuprofen 400 mg PO, or equivalent, for fever.
  - Oxygen and bronchodilators for mild bronchospasm.
- Resume the enoblituzumab infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to Grade 1. The rate may then be escalated to the original rate after 30 minutes, as tolerated. Consideration can be given to beginning all subsequent infusions at 50% rate and increasing as tolerated.
- Monitor for worsening condition. If symptoms recur, discontinue the enoblituzumab infusion; no further enoblituzumab will be administered at that visit.
- Prophylactic pre-infusion medications should be given prior to subsequent infusions of enoblituzumab.
  - Patients who experience Grade 2 infusion reaction, for subsequent doses of enoblituzumab, pre-medicate with diphenhydramine hydrochloride 25 to 50 mg IV/PO and acetaminophen 650 mg PO and/or ibuprofen 400 mg PO (or equivalent) at least 30 minutes before additional enoblituzumab administrations.
  - For patients with Grade 2 enoblituzumab infusion reactions, despite premedication with diphenhydramine and acetaminophen and/or ibuprofen

(or equivalent), corticosteroids (10 to 20 mg dexamethasone IV or equivalent) may be added to the premedication regimen for the next dosing of enoblituzumab. Reduce corticosteroid dosing by 50% for the subsequent dose and hold thereafter, if there are no reactions.

Grade 3 Infusion Related Reaction:

- STOP THE ENOBLITUZUMAB INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PATIENT.
- TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING – ASPIRATE RESIDUAL ENOBLITUZUMAB FROM THE PORT LUMEN.
- Administer diphenhydramine hydrochloride 25 to 50 mg IV, dexamethasone 20 mg IV (or equivalent), and other medications/treatment as medically indicated. Higher doses of corticosteroids (e.g., methylprednisolone 2 to 4 mg/kg IV or the equivalent) may also be considered for acute management.
- Consider administering, tocilizumab (an IL6 receptor antagonist) 4 mg/kg IV.
- IV fluids, supplemental oxygen, H2 blockers such as ranitidine and bronchodilators should be considered, as appropriate.
- If the Grade 3 infusion reaction occurs with any enoblituzumab dose, it will be discontinued for that day.
  - If symptoms have resolved to baseline within 12 hours, enoblituzumab may be infused at the next scheduled dose, with a 50% reduction of infusion rate. In addition, patients should be pre-medicated for this re-challenge and for any subsequent doses of enoblituzumab with the following: diphenhydramine hydrochloride 25 to 50 mg IV, acetaminophen 650 mg PO and/or ibuprofen 400 mg PO (or equivalent); corticosteroids should be considered as well (dexamethasone 10 to 20 mg IV or equivalent). Reduce corticosteroid dosing by 50% for the subsequent dose and hold thereafter, if there are no reactions.
  - Patients who have a Grade 3 infusion reaction that does not resolve within 12 hours despite medical management should be discontinued from enoblituzumab.
- Patients who experience a second Grade 3 infusion reaction to enoblituzumab at the time of re challenge of enoblituzumab will permanently discontinue enoblituzumab.

Grade 4 Infusion Related Reaction:

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PATIENT.

- TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING. ASPIRATE ENOBLITUZUMAB FROM THE PORT LUMEN
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 20 mg IV (or higher doses of steroids, e.g., methylprednisolone 2 to 4 mg/kg IV or the equivalent, as considered appropriate).
- Consider administering, tocilizumab (an IL6 receptor antagonist) 4 mg/kg IV.
- Give epinephrine or bronchodilators as indicated.
- Support ventilation and blood pressure as indicated.
- Patients who have a Grade 4 infusion reaction will permanently discontinue enoblituzumab.

7.3 Preparative Regimen (Day -5 and Day -4)

A lymphodepleting regimen of fludarabine and cyclophosphamide is given in the outpatient setting on two consecutive days. A minimum of 48 hours must be maintained between the last dose of fludarabine and the 1st dose of FT538 on Day 1.

Cohort 5 and Cohort 6 only: If there is unresolved toxicity associated with the enoblituzumab, the treatment plan may be delayed as needed; however, a minimum of 48 hours must be maintained between the last dose of fludarabine and the 1st dose of FT538 (Day 1).

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 2 consecutive days.

Cyclophosphamide 300 mg/m^2 is administered as a 2 hour intravenous infusion per institutional guidelines once a day on the same 2 days fludarabine is given.

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.

7.4 FT538 (Day 1, Day 8, and Day 15)

A minimum of 48 hours must separate the last dose of fludarabine and the 1st dose of FT538. The 1st dose of FT538 may be delayed for up to 7 days after the last dose of fludarabine if the study physician feels a delay is in the best interest of the patient. The 1st dose of FT538 equals Day 1. There is no Day 0.

A ±1 day window is permitted for subsequent infusions to accommodate scheduling issues.

7.4.1 Decision to Treat on Day of Planned FT538

If a patient experiences a dose limiting toxicity with the previous dose of FT538, FT538 is permanently discontinued.

Three weekly doses of FT538 are planned; however, if on the day of treatment, the study physician feels it is not in the best interest of the patient to receive treatment:

- The FT538 may be delayed for up to 48 hours adjusting future time points to maintain timing if subsequent FT538 is to be given OR
- The FT538 dose is skipped and the patient is scheduled for the next planned visit. Skipped dose(s) are not made up.

For AE(s) considered not related or unrelated to FT538, schedule modification of FT538 is not required if in the opinion of the treating investigator, such AE(s) do not represent a safety risk to the patient.

Additional modifications to the FT538 dosing schedule, including dosing delays, will be based on consultation between the treating investigator and the PI, and Fate Therapeutics, if applicable.

7.4.2 FT538 Intraperitoneal Infusion Guidelines

Pre-medications: Patients should be pre-medicated with acetaminophen 650 mg orally and diphenhydramine 25 mg orally before and 4 hours after the administration of FT538. Corticosteroids should not be used as pre-medication for FT538.

Vital Signs include oral temperature, blood pressure, heart rate, respiratory, and pulse oximetry. On days of FT538 administration, collect as follows: within 15 minutes prior to the infusion of FT538, after the final flush/prior to start of repositioning, and every 15 minutes (±5 minutes) for 1 hour from the end of the administration. The end of administration time is after the rinse step has been completed for the last administered bag of FT538.

FT538 Infusion guidelines: FT538 is provided in one or more cryopreserved bags depending on the patient's assigned FT538 cell dose.

FT538 must be administered using an IV administration set without an in line filter (filter is not required for IP administration). FT538 is administered as an IP infusion via gravity after any ascites or IP wash fluid has been drained.

After priming and set up have been performed, administer as follows:

1. Close all roller clamps on the infusion set.
2. Fully spike saline source container and prime the infusion set following the applicable package instructions.
3. Connect set to recipient.
4. Fully spike an inverted FT538 bag with the unused Y-lead. Do not spike FT538 bag while it is hanging.
5. Slowly open the roller clamp below FT538 bag and adjust for desired flow rate.
6. When FT538 bag is empty, close all clamps.
7. It is recommended each bag and tubing be flushed with up to 50 cc of room temperature normal saline; however, the flush volume may be adjusted at the discretion of the treating investigator. Close all clamps and invert FT538 bag 2-3 times to ensure thorough rinsing.
8. Open the roller clamp that is nearest to the subject and then slowly open the roller clamp below FT538 bag and adjust for desired flow rate.
9. When FT538 product container is empty, close the clamp below the FT538 bag.
10. If additional FT538 bags are to be infused, once the new FT538 bag is thawed, remove the empty FT538 bag and spike the new FT538 bag. Repeat Steps 1-9 for each additional bag.
11. Record the end of administration time after the rinse step has been completed for the last FT538 bag.

After the final flush, the patient is asked to change position at 15-minute intervals for two hours to ensure adequate intra-abdominal distribution. No attempt will be made to retrieve the infusate.

7.4.3 Monitoring During and Post-Infusion

Monitor the patient for signs of acute infusion related reaction during and after IP infusion. For IV infusion signs of a possible reaction are rigors and chills, rash, urticaria, hypotension, dyspnea, and angioedema. Abdominal pain and/or cramping was the most common adverse event with IP administration of other Fate NK products (FT516, NK100), and NK cell products in general (all given with IL-2).

If an acute infusion reaction of any grade occurs do not give any remaining bags of cells (if relevant). Refer to Table 1 for management guidelines based on infusion related reaction CTCAE v5 grading.

7.4.4 Potential Risks Associated with FT538

In this study FT538 is infused by intraperitoneal (IP) infusion. In our previous studies of IP infusion of NK cell products including Fate NK100 and FT516 (each given with IL-2) abdominal pain and cramping were observed in the majority of patients. Most were CTCAE 5 Grade 1 or Grade 2, with an occasional Grade 3 event. The pain usually was managed with oral and/or intravenous analgesics.

The following are potential risks of FT538 when given as an intravenous (IV) infusion. Refer to the current FT538 Investigator Brochure for a complete list of expected toxicities.

7.4.4.1 Acute Allergic/Infusion Reaction

Acute allergic/infusion reactions may occur with any treatment, including with the use of CY, FLU, and mAbs. Patient should be closely monitored for the occurrence of acute allergic/anaphylactoid infusion reactions such as rigors and chills, rash, urticaria, hypotension, dyspnea, and angioedema during and following completion of the infusion.

Acute allergic/infusion reactions may also be a manifestation of FT538 immunogenicity given that FT538 is an allogeneic cell product. Recommended guidelines for management of subjects who develop acute allergic/infusion reactions to FT538 are provided in Section 8.2.1 Table 1.

7.4.4.2 Immunogenicity Risks

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. In addition, FT538 immunogenicity may have an impact on FT538 PK, which in turn may have an impact on FT538 anti-tumor activity. Evidence of FT538 immunogenicity and its clinical impact will be monitored during the study. AEs arising from FT538 immunogenicity will be managed per institutional practice.

7.4.4.3 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 (AABB 2016).

7.4.4.4 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).

7.4.4.5 Cytokine Release Syndrome

CRS is a symptom complex associated with multiple therapeutic modalities, including mAbs and CAR T-cell therapies that arise from lymphocyte activation, which in turn results in the release of cytokines. Clinical manifestations of CRS include cardiac, gastrointestinal, hepatic, coagulation, renal, respiratory, skin, and constitutional (fever, rigors, headaches, malaise, fatigue, arthralgia, nausea, and vomiting) signs and symptoms. Treatment-emergent adverse events (TEAEs) that may be attributed at least in part to CRS include fever, febrile neutropenia, hypotension, acute vascular leak syndrome, renal failure, hypoxia, and pleural effusion. Because the signs and symptoms of CRS are not unique to CRS, other causes of fever, hypotension, and/or hypoxia must be excluded. Notably, bacteremia and other severe infections have been reported concurrent with and even mistaken for CRS (Lee et al. 2019). While CRS is a clearly defined syndrome with CAR T-cell therapy, it is generally not believed to be a toxicity associated with NK-cell therapies unless administered with systemic cytokines that may independently drive the proliferation and activation of CD8+ T cells, e.g., exogenous IL-15 (Cooley et al. 2019). To consistently characterize its severity, CRS should be graded according to ASTCT CRS consensus grading (Lee et al. 2019; Table 6). In addition to clinical manifestations, if CRS is suspected, CRP and ferritin levels should be assessed locally, and blood samples should be collected for central cytokine analysis per Section 10.2. Recommended guidelines for management of subjects who develop CRS are provided in Section 8.2.2.

7.4.4.6 Tumor Lysis Syndrome

TLS is a possible fatal risk associated with anti-tumor therapy in both hematologic and solid tumors, especially with large tumor burden (Mirrakhimov et al. 2014). 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 laboratory changes that include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. TLS has been reported to occur within 7 days following chemotherapy across various solid tumor settings, with 10 published reports of TLS cases in patients with gynecological cancer (Mirrakhimov et al. 2014). One case of fatal metabolic syndrome compatible with TLS was reported following NK-cell therapy in a patient with ovarian cancer 5 days after receiving CY (Geller et al. 2011). Prophylaxis for and management of TLS should be done in accordance with standard institutional practice. Following FT538 administration, subjects should be followed closely for signs and symptoms of TLS, with regular clinical (including telemetry where applicable) and laboratory monitoring. Laboratory abnormalities suggestive of TLS should prompt immediate action by the treating clinicians, and TLS should be treated aggressively per institutional practice.

7.4.4.7 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Neurologic toxicity has been reported frequently with blinatumomab and CAR T-cell therapy (Blincyto® USPI; Kochenderfer et al. 2015; Maude et al. 2014). The etiology of toxicity in these settings is not known and may not be responsive to cytokine-directed therapy such as tocilizumab but has generally improved with treatment discontinuations and corticosteroids (Blincyto USPI; Goebeler et al. 2016; Kochenderfer et al. 2015) While CNS toxicity is a clearly defined syndrome associated with CAR 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 et al. 2019). Nervous system toxicities following CD19 CAR T-cell therapy is characterized by encephalopathy, confusion, delirium, aphasia, obtundation, and seizures (Kymriah USPI; Yescarta USPI). Cases of cerebral edema have also been reported (Brudno and Kochenderfer 2016). To consistently characterize its severity, neurotoxicity must be graded using ASTCT consensus for grading ICANS (Lee et al. 2019; Table 4). Recommended guidelines for management of subjects who develop neurotoxicity are provided Section 8.2.3.

7.4.4.8 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 et al. 2017). Acute GvHD assessments will

be performed with assignment of the overall severity based on the CIBMTR acute GvHD grading scale (Table 5). Management of GvHD should be done in accordance with local institutional practice.

Refer to Section 8 for Management of Selected Adverse Events including dose delays and modifications.

7.5 Monitoring for Dose Limiting Toxicities and Excessive Toxicity

Toxicity and adverse events is classified and graded according to NCI's Common Terminology Criteria for Adverse Events V 5.0 (CTCAE) unless otherwise noted in Section 11.

All patients are monitored for dose limiting toxicity (DLT) and excessive toxicity during the 1st 28 days after the 1st FT538 infusion. For Dose Cohorts 5 and 6, the monitoring begins with enoblituzumab and continues for 28 days after 1st FT538.

In addition, during the fast-track dose escalation only (Stage 1, Step 1), patients also are monitored for the pre-defined treatment emergent events of within 28 days after the 1st FT538 infusion (for Cohort 5 and 6, DLT assessment starts with enoblituzumab and continues for 28 days after 1st FT538):

- Grade 3 abdominal pain, not attributable to the cancer, within 28 days after the 1st FT538 infusion lasting more than 48 hours despite treatment with standard analgesics

or

- Grade 3 infusion related reaction within 24 hours after the 1st FT538 infusion in any Dose Cohort or 1st enoblituzumab infusion in DC 5 or DC 6 and symptoms resolve to baseline within 12 hours.

Dose Limiting Toxicity (DLT) is defined as any treatment emergent toxicity at least possibly related to the investigational product(s) meeting one of the following criteria based on CTCAE v5 within 28 days (within 14 days for ascites) after the 1st FT538 infusion:

- Grade 3 organ disorders (pulmonary, hepatic, renal, or neurologic) and lasting more than 72 hours
- Grade 3 abdominal pain not attributable to cancer lasting more than 4 consecutive days and not controlled by standard analgesics
- Grade 3 or greater ascites within 14 days after FT538 administration in patients who had no ascites or Grade 1 ascites at enrollment and is not attributable to disease progression
- Any non-hematologic Grade 4 or 5 toxicity

- Grade 4 neutrophil count decreased that persists at Day 28 despite use of growth factor support

All patients are monitored for DLT events during the 1st 28 days after the initial FT538 infusion. The DLT period does not end until:

1) results from lab work drawn Day 29 (+3 days) does not meet a DLT and

2) a patient assessment on Day 29 (+3 days), confirms no new DLT since the last assessment or ongoing DLT events.

Monitoring for Excessive Toxicity (all patients)

Monitoring guidelines are in place for excessive toxicity. Refer to Section 14.4 for complete details:

- Excessive dose limiting toxicity (DLT) events - the trial will be stopped if the posterior probability that the lowest dose is unacceptably toxic (> 25% of patients) is greater than 80% as determined by the study statistician.
- Grade 3 or greater Infusion Related Reaction through Day 28 in association with any FT538 infusion in any Dose Cohort or in association with enoblituzumab in Dose Cohort 5 and 6.
- Early Death (Grade 5 Event) within 28 days after the last dose of FT538.

7.6 Supportive Care

Throughout the study, the investigator may prescribe any concomitant medications not otherwise described as cautionary therapy or prohibited therapy (refer to Section 7.7) or treatment deemed necessary to provide adequate supportive care.

Supportive care may include antibiotics, analgesics, transfusions, growth factors, etc. Only irradiated blood products should be used to minimize the risk of transfusion-associated GvHD.

7.7 Cautionary and Prohibited Therapy

Systemic corticosteroids should be avoided during the treatment, unless absolutely required, because they may inhibit NK-cell function. Because of their deleterious effect on NK-cell-based therapy, corticosteroids as pre-medication for CY and FLU should be avoided unless considered necessary by the investigator and should not be administered within 3 days before or within 14 days after FT538 administration.

Intravenous glucocorticoid as pre-medication for cyclophosphamide, fludarabine, and enoblituzumab may be administered per the USPI or institutional guidelines. Methylprednisolone should be used as the preferred glucocorticoid pre-medication given its shorter half-life. Long-acting corticosteroids, such as dexamethasone, should not be used.

Glucocorticoids must not be used as pre-medication for FT538.

Any antineoplastic agent for therapeutic intent other than protocol-designated study treatment(s) is prohibited until after the 1st disease reassessment.

7.8 Duration of FT538 Treatment and Possible Retreatment

Treatment with FT538 consists of a single treatment course of 3 weekly doses on Day 1, Day 8, and Day 15 in the absence of a dose limiting toxicity or contraindication for treatment as detailed in Section 7.4.1. For participants assigned to Dose Cohort 5 or Dose Cohort 6, enoblituzumab may continue every 3 weeks per Section 7.9.

If a patient has clinical benefit (SD, PR or CR per RECIST and no decline from the baseline performance status) at the 1st disease re-assessment around Day 36, they may be eligible to repeat the treatment using their same Dose Cohort provided the criteria in Section 5.3 is met.

Retreatment has no effect on the primary and secondary analysis; however, adverse events (safety data) are documented in 2021LS103R and reported per Section 11. Study endpoints progression free survival and overall survival remain at 6 months and 12 months from the 1st dose of FT538 (Day 1).

7.9 Duration of Enoblituzumab (COHORT 5 or 6 ONLY)

Enoblituzumab may continue until disease progression, unacceptable side effects, patient refusal or non-compliance, or felt by the treating investigator to no longer be of benefit to the patient.

If ongoing at the end of the planned study participation at 12 months, enoblituzumab may continue beyond 12 months in the absence of disease progression and unacceptable toxicity.

An End of Treatment visit should occur approximately 3 weeks after the last dose of enoblituzumab.

7.10 Duration of Study Participation

Patients will be followed for disease response per standard of care until disease progression/relapse or the start of a new treatment, and then survival only for 12 months from the 1st FT538 infusion unless:

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

Research related safety samples for Fate are collected per Section 10.2 at a standard of care visit closest to the targeted timepoint for those continuing their care at the University of Minnesota.

If a patient is not returning to the University of Minnesota for care, disease response (if progression was not previously established) and survival information may be obtained from the local medical doctor or other sources, such as public records.

If applicable, enoblituzumab may continue every 3 weeks beyond 12 months in the absence of disease progression and unacceptable toxicity.

Any patient receiving at least one dose of FT538 is followed for up to 15 years for late effects and survival. During the 1st year LTFU data is collected and recorded under the LTFU study. After the final treatment study endpoint at 12 months, the patient continues on the long-term follow-up protocol for safety, anti-tumor activity, and survival for up to 15 years from the 1st FT538 infusion.

8 Management of Adverse Events Related to FT538

Refer to Appendix III for expected toxicities of the lymphodepleting regimen and Section 9 for management of toxicities related to enoblituzumab.

8.1 Management Guidelines for Specific FT538 Adverse Events

In this study FT538 is infused intraperitoneally. In our previous studies of intraperitoneal (IP) Fate NK100 and FT516 (each given with IL-2) abdominal pain and cramping was seen in association with the administration of the investigational product. The pain was usually managed with oral and/or intravenous analgesics.

Recommended guidelines for the management of specific AEs associated with intravenous (IV) administration are outlined below.

For cases in which management guidelines are not covered in the protocol or current local prescribing information, participants should be managed as deemed appropriate by the investigator according to best medical judgement.

8.1.1 Acute Allergic/Infusion Reactions

Acute allergic/infusion reactions may occur with any treatment, including with the use of CY, FLU, and enoblituzumab.

Patients are monitored for acute infusion related reactions associated with intravenous infusions including rigors and chills, rash, urticaria, hypotension, dyspnea, and angioedema during and after IP infusion

The recommended management of acute infusion or allergic reactions that occur during FT538 administration is described in Table 1 based on intravenous infusion.

Appropriate medical care beyond what is described in the protocol should be instituted as per the respective current local prescribing information or standard institutional practices. Because they may inhibit NK-cell function, systemic corticosteroids should be avoided unless absolutely required for the management of acute allergic/infusion reactions, as determined by the investigator.

Table 1: Recommended Guidelines for the Management of Acute Allergic/Infusion Reaction with FT538 Administration (Based on IV Infusion)

Grade based on CTCAE v5	Management
Any Grade	• Interrupt FT538 administration. • Manage symptoms, e.g., with antihistamines, antipyretics, and analgesics, according to standard institutional practice standards
Grade ≤3	• 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 of Grade ≤3 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 Sponsor for further instruction. − Additional bags may not be administered to make up for FT538that 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 PI or designee for further instructions. − 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.
Grade 4	• 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 the PI or designee for further instructions.

8.1.2 Cytokine Release Syndrome or CRS-Like Syndrome

If CRS is suspected or diagnosed, CRP, ferritin, IL-6 levels should be assessed.

If indicated by the presence of medically significant symptoms and/or high IL-6 levels or any symptoms requiring intervention, corticosteroids are the first line of treatment.

To consistently characterize its severity, CRS should be graded according to ASTCT CRS consensus grading (Lee et al. 2019; Table 2). In addition to clinical manifestations, if CRS is suspected, CRP, ferritin, IL-6 levels should be assessed.

Recommended guidelines for management of subjects who develop CRS are provided in Table 3.

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 10.1. In addition, a serum sample should be collected for an IL-6 level at the time of any change (increase or decrease) in the CRS grade. Because patients may be outpatients any missed collection time points will not be a protocol deviations.

Table 2. ASTCT Consensus Grading for Cytokine Release Syndrome[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/without 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)

Source: Lee et al. 2019

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. Constitutional symptoms of CRS, such as myalgia, arthralgia, and malaise, are by themselves nonspecific; however, when coincident with fever in the expected timeframe, the etiology of CRS is more likely. In subjects who have CRS then receive

antipyretics or anti-cytokine therapy such as tocilizumab or corticosteroids, 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.
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, Version 5.

Management of CRS should follow the recommended management algorithm provided in Table 3 (Neelapu 2018) and/or institutional practice.

Table 3: Recommendations for the Management of Cytokine Release Syndrome

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

Table 3: Recommendations for the Management of Cytokine Release Syndrome		
Grade	**Sign/Symptom**	**Management**
	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

Source: Neelapu et al. 2018; Actemra® USPI.

CRS = cytokine release syndrome; ICU = intensive care unit; IV = intravenous, USPI = United States Prescribing Information

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.

8.1.3 Neurotoxicity

To consistently characterize its severity, neurotoxicity must be graded using the ASTCT guidelines for grading ICANS provided in Section 11 based on the Immune

Effector Cell-Associated Encephalopathy (ICE) score and Table 4. Per Section 11 an assessment is done prior to each FT538, 2 to 4 hours later, and prior to discharge if the post-infusion stay extends beyond 4 hours.

Determinants of the ICE score are:

- **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

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; Appendix IV: Table A-1, Table A-2, and Table A-3) and/or institutional practice.

Table 4: 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; Appendix IV: Table A-1, Table A-2, and Table A-3) and/or institutional practice.

8.1.4 Graft versus Host Disease

Acute GvHD will be assessed according to criteria established by the CIBMTR Scale (Table 5). Management of GvHD should be done in accordance with local institutional practice.

Table 5: Acute GvHD Scoring System for Individual Organs: CIBMTR Scale

	Skin	Liver	Gut
stage			
1	Rash on < 25% of skin[a]	Bilirubin 2-3 mg/dL[b]	Diarrhea >500 mL/day[c] or persistent nausea[d]
2	Rash on 25%-50% of skin	Bilirubin 3-6 mg/dL	Diarrhea >1000 mL/day
3	Rash on >50% of skin	Bilirubin 6-15 mg/dL	Diarrhea >1500 mL/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus
Grade			
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	---	Stage 2-3 or	Stages 2-4
IV	Stage 4	Stage 4	---

Source: CIBMTR 2020.

a Use “Rule of Nines” or burn chart to determine extent of rash.
b Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.
c Volume of diarrhea applies to adults. For pediatric subjects, the volume of diarrhea should be based on body surface area. Downgrade one stage if an additional cause of diarrhea has been documented.
d Persistent nausea with histologic evidence of GvHD in the stomach or duodenum.
e Criteria for grading given as minimum degree of organ involvement required to confer that grade.
f Grade IV may also include lesser organ involvement with an extreme decrease in Performance Status.

CIBMTR = Center for International Blood and Marrow Transplant Research GvHD = Graft-versus-host disease

9 Management of Selected Expected Toxicities Associated with Enoblituzumab (Dose Cohort 5 and 6)

Refer to Appendix III for expected toxicities of the lymphodepleting regimen.

9.1 Known Infusion Related Reaction (IRR) to Enoblituzumab

Refer to Section 7.2.3 for the management of enoblituzumab related infusion reaction.

To date, the most important safety risk that has been identified with enoblituzumab is infusion-related reactions (IRR), including reactions known as cytokine release syndrome (CRS) due to the release of small proteins (cytokines) from the cells. IRRs are generally temporary effects due to a drug that may occur during or shortly after infusion of the drug.

Signs and symptoms of an infusion-related reaction may include fever, chills, nausea, vomiting, headache, muscle stiffness, rash, itching, low blood pressure, and difficulty breathing. Infusion related reaction or cytokine release syndrome was reported in 48.5% of 373 patients in MacroGenics-sponsored clinical trials of enoblituzumab, with 42.1% of patients experiencing IRR/CRS that were mild to moderate in severity. Events of IRR/CRS ≥ Grade 3 in severity were seen in 6.4% (n=24) of patients. Two of these patients with a ≥ Grade 3 IRR/CRS event experienced an event of life-threatening IRR/CRS (1 received enoblituzumab in combination with ipilimumab and 1 received enoblituzumab in combination with pembrolizumab). Refer to the Reference Safety Information of the current Enoblituzumab Investigator's Brochure.

9.2 Most Common Side Effects of Single Agent Enoblituzumab

General risks associated with drugs similar to enoblituzumab:

- Infusion reactions – Refer to Section 7.2
- Immune-related side effect:
    - Pneumonitis (inflammation in the lungs)
    - Colitis (inflammation of the colon)
    - Hepatitis (inflammation of the liver)
    - Hypothyroidism
    - Adrenal insufficiency

- Kidney problems.
- Encephalitis (inflammation of the brain)
- Skin problems, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
- Myocarditis (inflammation of the heart muscle)
- Other issues including changes in eyesight, severe muscle or joint pain or weakness, and/or anemia.

The following were the most common side effects that were considered related to single-agent enoblituzumab administration and were seen in at least 1 of 10 adult participants. As of 15 June 2021 Investigator's Brochure, these side effects have been generally mild or moderate.

Very Common (≥10%):

- Infusion related reactions (IRRs) including CRS – Refer to Section 9.1
- Fatigue
- Nausea
- Chills
- Vomiting

Common

- Fever
- Flu like symptoms
- Decreased appetite
- Headache
- Pruritus

10 Schedule of Patient Activities

Virtual visits may replace in person clinic visits as relevant. Lab work and disease reassessments must be performed at the enrolling site, unless other arrangements are permitted as discussed with the study PI. In the event re-consent is required, it may be performed electronically (e-consent).

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. If receiving enoblituzumab, at least 1 day must separate the dose of enoblituzumab and the start of the lymphodepletion chemotherapy. The 1st dose of FT538 may be delayed for up to 7 days after the last dose of fludarabine in the event FT538 cannot be given as planned. Day 1 is the day of the 1st FT538 infusion. There is no Day 0.

For Dose Cohorts 5 and 6 only: The 1st dose of enoblituzumab is given on Day -6 before the start of the cyclophosphamide/fludarabine. Subsequent doses are given starting on Day 22 and every 3 weeks (±2 days) until no longer of benefit. Refer to Section 7.2.1 if the patient has an infusion related reaction with Dose 1 and it is recommended Dose 2 be given with steroid containing pre-medication. Adjustment to the enoblituzumab dosing to permit steroid use is not a protocol deviation.

A window of ±1 day for scheduling issues is permitted for Day 1, Day 8, Day 15, and Day 22.

As detailed in Section 7.4.1, if on the day of the planned treatment, the study investigator feels it is not in the best interest to treat the patient, the FT538 may be:

- Delayed for up to 48 hours adjusting future time points to maintain timing OR
- Skipped and the patient scheduled for the next planned visit. Skipped dose(s) are not made up.

All patients are monitored for dose limiting toxicity (DLT) during the 1st 28 days after the initial FT538 infusion. The DLT period does not end until:

1) None of the bloodwork results from the labs drawn Day 29 (+3 days) meet the definition of a DLT event and
2) A patient assessment on Day 29 (+3 days), confirms no new DLT since the last assessment or ongoing DLT events.

Assessments to be performed after Day 29 through the End of Treatment visit may be done ±3 days of the targeted date. In addition, targeted days may be altered as clinically appropriate.

The same guidelines apply during retreatment with retreatment Day 29 (rDay29) being the final visit tied to retreatment.

During follow-up, until disease progression or the start of a new treatment, the standard of care disease reassessment closest to the targeted follow-up date should be used for the Month 3, 6, 9, and 12 follow-up time points. Once disease progression is confirmed, follow-up is for survival only. Note: these same time points apply to patients who are continuing enoblituzumab, as disease status and survival are secondary endpoints.

Standard of care (SOC) assessments and procedures are considered part of good clinical care and are charged to the patient and their health plan/health insurance.

10.1 Required Standard of Care Activities Refer to the introduction in Section 10 regarding timing of treatment.

	Screening[1] Within 28 days prior the 1st dose of CY/FLU or Eno (if applicable)	Prior to the 1st dose of CY/FLU or Eno (if applicable)	Enoblituzumab (Eno) (Day -6) Cohort 5 and cohort 6 only	CY/FLU		Day 1	Day 3	Day 8	Day 15	Day 22	Day 29 (end of DLT period)		Day 36 End of Treatment (EOT) visit for FT538, unless retreated[9]	for Cohort 5 and 6 only while receiving Enoblituzumab		Follow-up all patients 3, 6, 9 and 12 months from Day 1[5]
				#1 (Day -5)	#2 (Day -4)	FT538 #1		FT538 #1	FT538 #3	Eno #2				Day 43 and every 3 weeks	End of Treatment visit[10]	
Consent	X															
Assess for Eligibility	X															
Medical History	X												X			
Review of concurrent medications	X												X	X		
Physical Exam	X										X		X	As needed	X	
Provider Assessment	X		X	X	X	X	X	X	X	X	X		X	X	X	
Determine if retreatment with FT538 is an option, if yes refer to Section 10.3													X[9]			
Weight	X		X	X		X[8]	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X	X	
Height	X															
Vitals and Pulse Oximetry	X		X[6]			X[6]		X[6]	X[6]	X	X			X		
GOG Performance Status	X												X			
ICANS (neurotoxicity) monitoring[7]			X			X[7]	X	X[7]	X[7]	X	X		X			
Toxicity Assessment: observed, patient reported or eMR abstraction (refer to Section 11.2 for AE documentation requirements)		X	X			X	X	X	X	X	X		X	X	X	
Survival Status																X
CBC, diff, plt	X		X			X		X	X	X	X	X	X	X	X	
Basic metabolic panel (BMP)[3]						X		X								
Comprehensive metabolic panel (CMP) or equivalent[4]	X		X	X					X	X	X	X	X	X	X	
CRP and Ferritin (SOC)[12]			Perform CRP and Ferritin 3 times weekly if CRS is suspected or diagnosed per Section 8.2.2.													
CA-125	X												X			X[5]
Urine or serum pregnancy test[11]	X															
eGFR	X															
Disease staging by RECIST	X												X			X[5]
CT or PET-CT of chest, abdomen and pelvis	X												X			X[5]
Brain CT or MRI	X[2]															
PFTs	X[2]															
12-lead EKG	X															
LEVF (ECHO, MUGA, or cardiac MRI)	X															
IP catheter placement / removal if no retreatment		X[13]											X			

Shaded columns apply to Dose Cohorts 5 and 6 only.

1 For screening, prior disease assessments may be used if they were performed within 42 days of the 1st FT538 infusion in the absence of intervening anti-cancer therapy. Consent is exempt from 28 day limit - may be performed at any time prior to starting study related activity, labs for eligibility and pregnancy testing must be repeated prior to the 1st dose of CY/Flu or enoblituzumab if > 14 days since done for eligibility.

2 perform only if known history or as medically indicated

3 basic metabolic panel consists of BUN, creatinine, calcium, glucose, lytes (CO2, Cl, Na, K)

4 comprehensive metabolic panel consists of albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, creatinine, glucose, electrolytes (CO2, Cl, Na,, K), total bilirubin, and total protein

5 Disease restaging per standard of care every 3 months until disease progression or start of a new treatment then follow for survival only for 12 months from the 1st FT538. Imaging/CA-125 closest to the targeted follow-up date should be used for Month 3, 6, 9, and 12 follow-up. Note: these same time points apply to patients who are continuing enoblituzumab as disease status and survival are secondary endpoints.

6 **Additional vital sign timepoints on days of investigational product administration:**
Vital signs for FT538 - include oral temperature, blood pressure, heart rate, respiration rate, and pulse oximetry. On days of FT538 administration, collect as follows: within 15 minutes prior to infusion of FT538, after the final flush/prior to repositioning and every 15 minutes (±5) minutes for 1 hour following the end of infusion of the last administered bag of FT538.
Vital signs for enoblituzumab – include oral temperature, blood pressure, heart rate, respiration rate. On days of enoblituzumab administration, collection as follows: upon arrival, within 15 minutes prior to start of the enoblituzumab, every 15 minutes (± 5 minutes for the first hour of the infusion, every 30 minutes (±5 minutes) thereafter until infusion end, upon discontinuing the infusion, and before the patient is discharged from the clinic.

7 Neurotoxicity will be monitored using the ASTCT guidelines for grading ICANS based on the criteria in Section 8.2.3. ICANS monitoring will occur just prior to start of lympho-conditioning, at specified time points, and as needed in to document complete resolution to baseline status. **On FT538 dosing days, assessment for ICANS should be done prior to infusion, 2 to 4 hours after FT538 administration and at time of discharge the post-infusion extends beyond 4 hours.** Unscheduled assessments should be performed if new or worsening ICANS is suspected. In cases of documented changes in the ICANS grading, follow-up assessments should be performed until resolution to baseline or patient discontinuation from the study, whichever occurs earlier. Refer to Section 8.2.3 for details.

8 To monitor for vascular leak syndrome per Section 11.2.

9 Retreatment may be an option for patients with stable disease or better based on the Day 36 reassessment. Refer to Section 5.3, Section 6.3, and Section 7.8 for additional information.

10 Cohort 5 and cohort 6 - End of Treatment visit approximately 3 weeks (± 8 days) after the last dose of enoblituzumab

11 Person of childbearing potential and still has the anatomy (uterus and ovaries) to get pregnant must have a negative pregnancy test (urine or serum) within 14 days of 1st dose of CY/FLU or Eno (if applicable).

12 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. In addition, a serum sample should be collected for an IL-6 level at the time of any change (increase or decrease) in the CRS grade. Because patients may be outpatients any missed collection time points will not be a protocol deviations.

13 If the IP catheter cannot be placed by interventional radiology, the patient will be taken off study per Section 6.4.

10.2 Research Related Evaluations

Shaded columns apply to Dose Cohorts 5 and 6 only.

Refer to Section 10.3 for research related activities during retreatment.

	Baseline: Prior to the 1st dose of CY/FLU or Eno (if applicable))	Prior to enoblituzumab (Day -6) Cohort 5 and Cohort 6 only	Prior to CY/Flu chemo	Day 1	Day 3	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43 Cohort 5 and 6 only	Research Sample Drawing Coincides with a SOC visit closest to the targeted time point			
												3 months from Day 1	6 months from Day 1	9 months from Day 1	12 months from Day 1
Enoblituzumab (Cohort 5 and 6 only)		X						X			X				
FT538 infusion				X		X	X								
Six 10 ml green top tubes – collect prior to the day's treatment (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X (30 ml)	X (30 ml)	X (30 ml)	X (30 ml)
One 10 ml of red top tube – collect prior to the day's treatment (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP and ferritin to FV lab	X								X						
PRA anti-HLA antibodies to FV lab	X									X					
IP fluid (ascites preferred over washings) – collect in a urine or similar container prior to the day's treatment (if applicable) Refer to Section 10.2.1	At time of IP catheter placement			X		X	X	X	X	X[1]					
Tumor biopsy by IR (if feasible) 6 cores (5-10 mm) preferred but less is acceptable – to BioNet	At time of IP catheter placement									X[1]					
Complete Data collection for LTFU study												X	X	X	X
Safety Samples for Fate 1 x 3 ml red top serum tube 1 x 10 ml green top tube – store frozen and batch ship to Fate	X											X	X	(not collected at 9 months)	X

1 - at time of IP catheter removal (Day 36 if no retreatment or at time of IP catheter removal if retreatment)

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

Note: if a patient is not abiding by the required clinical care calendar (Section 10.1), the collection schedule of research related samples may be altered 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 timepoint.

All research samples go to the Masonic Cancer Center's Translational Therapy Lab (TTL) unless otherwise indicated. Baseline and Day 29 ferritin/CRP and PRA anti-HLA antibodies testing are charged to research but run in the treatment center's clinical lab. If additional ferritin and/or CRP levels are collected as part of good medical care (i.e. development of signs of CRS) they are to be charged as standard of care.

For all patients receiving FT538, samples as designated in the above table are shipped from TTL to Fate.

For Cohorts 5 and 6 only, serum and ascites samples (not IP wash samples) are provided to MacroGenics by TTL to determine enoblituzumab levels.

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, blood and/or IP fluid may be collected at up to 3 additional time points that are not specified above.

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

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

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

10.2.1 Intraperitoneal (IP) Fluid Collection

Ascites is preferred and a collection of such should be attempted first. It is recommended to obtain a minimum of 200cc and up to 500cc if ascites is present. Lower or higher volumes are acceptable. Any ascites collected, regardless of the volume, will be submitted to TTL as a separate sample from peritoneal washings if both obtained. The higher the volume of ascites submitted, the better the yield of Tumor Ascites Lymphocytes (TALs).

If ascites is drained for clinical care at other times during this timeframe, a sample (up to 500 cc) may be submitted to TTL as an additional time point.

If no ascites is present or less than 50cc is collected, peritoneal washings will be performed. A volume of 250cc of room temperature NS will be infused into the abdomen. After infusion the patient will be asked to change position (right lateral, left lateral, Trendelenburg (feet higher than head by 30 degrees), reverse Trendelenburg) at 5-minute intervals to ensure adequate intra-abdominal distribution. Fifty (50) cc of infusate will then be retrieved through the indwelling catheter.

If a minimum of 50cc of infusate is not retrieved, another 250 cc of NS will be infused and the above process repeated. If after this 50cc of infusate have not been retrieved, the process will be terminated, however, any amount of infusate that is retrieved should be sent to TTL for testing.

10.2.2 Tumor Biopsies

Tumor biopsies will be performed if feasible. The inability or failure to do a biopsy will not be considered a protocol deviation. It is preferred that 6 cores (5-10 mm) be collected. It is understandable that it may not always be possible to obtain 6 cores and in such cases testing will be prioritized based on the number of cores received. The inability to collect any tumor samples or an insufficient amount will not be considered a protocol deviation.

Samples go to BioNet and handled per the contract with BioNet.

10.3 Retreatment Required Clinical Care and Research Related Evaluations

Retreatment is offered to a sub-set of patients whose 1st disease re-assessment shows stable disease or better on a compassionate basis. Retreatment does not contribute to primary or secondary endpoints. Flexibility for the start of the retreatment course is permitted

Retreatment requires signing of the retreatment consent and confirmation of ongoing eligibility per Section 5.3. Retreatment is a separate protocol entry in OnCore (CPRC# 2021LS103R) which releases a new set of case report forms specific to retreatment. Flexibility with the start of the retreatment course is permitted.

After rDay 29, patient follow-up continues per Section 10.1 and Section 10.2 beginning with the 3 month post Day 1 follow-up.

Shaded columns apply to Dose Cohorts 5 and 6 only.

	Additional retreatment activities (overlap with Day 36 visit)	Enoblituzumab (rDay -6/Day 43 visit) Cohort 5 and cohort 6 only	CY/FLU		rDay 1	rDay 3	rDay 8	rDay 15	rDay 22	rDay 29
			#1 rDay -5	#2 rDay -4						
Consent with retreatment consent and enroll in study 2021LS103R	X									
Confirmation of ongoing eligibility per Section 5.3	X									
Medical History										
Provider Assessment		X	X	X	X	X	X	X	X	
Weight		X	X		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Vitals and Pulse Oximetry		X[1]	X		X[1]		X[1]	X[1]	X	X
GOG Performance Status										X
ICANS (neurotoxicity) monitoring)[2]		X[2]			X[2]	X	X[2]	X[2]	X	X
Toxicity Assessment: observed, patient reported or eMR abstraction (refer to Section 11.2 for AE documentation requirements)		X			X	X	X	X	X	X
CBC, diff, plt		X	X		X	X	X	X	X	X
Basic metabolic panel (BMP)					X	X				
Comprehensive metabolic panel (CMP) or equivalent		X	X				X	X	X	X
Urine or serum pregnancy test										
eGFR										
Research Related Activities										
Enoblituzumab IV (Cohort 5 and Cohort 6 only)		X							X	
FT538 IP					X[1]		X[1]	X[1]		
Six 10 ml green top tubes – collect prior to the day's treatment (if applicable)		X	X		X	X	X	X	X	X
One 10 ml of red top tube – collect prior to the day's treatment (if applicable)		X	X		X	X	X	X	X	X
PRA anti-HLA antibodies to FV labs									X	
ferritin, CRP to FV lab										X[5]
IP fluid (ascites preferred over washings) – collect in a urine or similar container prior to the day's treatment (if applicable) Refer to Section 10.2.1					X	X	X	X	X	X
Tumor biopsy by IR (if feasible) at time the IP catheter is removed - 6 cores (5-10 mm) preferred but less is acceptable – to BioNet										X[6]

1 **Additional vital sign timepoints on days of investigational product administration:**
Vital signs for FT538 - include oral temperature, blood pressure, heart rate, respiration rate, and pulse oximetry. On days of FT538 administration, collect as follows: within 15 minutes prior to infusion of FT538, after the final flush/prior to repositioning and every 15 minutes (±5) minutes for 1 hour following the end of infusion of the last administered bag of FT538.
Vital signs for enoblituzumab – include oral temperature, blood pressure, heart rate, respiration rate. On days of enoblituzumab administration, collection as follows: upon arrival, within 15 minutes prior to start of the enoblituzumab, every 15 minutes (± 5 minutes for the first hour of the infusion, every 30 minutes (±5 minutes) thereafter until infusion end, upon discontinuing the infusion, and before the patient is discharged from the clinic.

2 Neurotoxicity will be monitored using the ASTCT guidelines for grading ICANS based on the criteria in Section 8.2.3. ICANS monitoring at specified time points, and as needed in to document complete resolution to baseline status. **On FT538 dosing days, assessment for ICANS should be done prior to infusion, 2 to 4 hours after FT538 administration and at time of discharge the post-infusion extends beyond 4 hours.** Unscheduled assessments should be performed if new or worsening ICANS is suspected. In cases of

documented changes in the ICANS grading, follow-up assessments should be performed until resolution to baseline or patient discontinuation from the study, whichever occurs earlier. Refer to Section 8.2.3 for details.

3 To monitor for vascular leak syndrome per Section 11.2.

4 Person of childbearing potential and still has the anatomy (uterus and ovaries) to get pregnant must have a negative pregnancy test (urine or serum) within 14 days of treatment start on the retreatment protocol.

5 rDay 29 ferritin and CRP is paid for by the study – if CRS occurs, additional ferritin and CRP levels are done as part of clinical care per Section 10.1 as detailed in Section 8.2.2.

6 Remove IP catheter after the Day 29 sample or sooner if warranted.

11 Event Monitoring, Documentation, and Reporting

FT538 is considered an investigational product for all patients.

Enoblituzumab is an investigational product for patients treated in Dose Cohort 5 or Cohort 6.

CY/FLU are study drugs.

Adverse Reactions will be reported to the FDA per 21 CFR 312.32.

Toxicity and adverse events is 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 (2019). Refer to Section 8.2.2 Table 2.

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

11.1 Event Terminology

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

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 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 adverse reaction, which means any adverse event caused by a drug.

Serious Adverse Event or Serious Suspected Adverse Reaction: An adverse event or suspected adverse reaction 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

Unexpected Adverse Event or Unexpected Suspected Adverse Reaction (SUSAR): 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: IBs are available for both investigational products (FT538 and enoblituzumab). The current USPI is the source of expected adverse events for the study drugs (cyclophosphamide and fludarabine).

Expedited (Rapid) Reporting: Certain events may require rapid notification to entities providing patient safety oversight (e.g. IRB). Refer to Section 11.5.

11.2 Event Monitoring and Documentation Requirements

Monitoring for adverse events begins with the insertion of the IP catheter. Between the time of consent signing and the 1st dose of CY/FLU or Eno (if applicable), only events directly related to the study and result in the inability to begin study treatment will be documented.

Monitoring continues through the Dose Cohort specific End of Treatment visit.

Note: if a patient is not abiding by the planned treatment schedule, the documentation of adverse events may be altered 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 timepoint.

The toxicity associated with the cyclophosphamide and fludarabine (CY/FLU) preparative regimen is well known and will not be documented unless the event meets the definition of a serious adverse event. Potential risks of CY/FLU are detailed in Appendix III.

Therefore, adverse event documentation for the purposes of this study will focus on the following events:

- Adverse events of special interest (AESI) requiring targeted monitoring including infusion related reactions (IRR), neurotoxicity, vascular leak syndrome, and cytokine release syndrome. Refer to Section 11.1 for timing/details.
- Any event within 28 days of the 1st FT538 infusion meeting the definition of dose limiting toxicity or for Step 1 only, a pre-defined adverse event per Section 11.3.
- Any event meeting the definition of a serious adverse event, regardless of attribution through the Dose Cohort specific End of Treatment visit and then upon knowledge if felt related to the study treatment.
- All Grade 3 and 4 adverse events regardless of attribution.
- Grade 2 adverse events felt possibly, probably or related to either enoblituzumab or FT538.

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 11.3.

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 targeted 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.

11.3 Dose Limiting Toxicity Event/Stopping Rule Documentation and Reporting

The following events require special documentation and reporting in addition to recording as an adverse event.

11.3.1 During Fast-Track Enrollment Only

During Stage 1, Step 1 of fast-track enrollment only, the 1st patient experiencing a pre-defined treatment emergent adverse event within 28 days of the 1st FT538 dose triggers a change to 3 patients per cohort (Stage 1, Step 2).

Pre-defined treatment emergent adverse events only are used for assessment in the single patient dose cohorts.

- Grade 3 abdominal pain, not attributable to the cancer, within 28 days after the 1st FT538 infusion lasting more than 48 hours despite treatment with standard analgesics

or

- Grade 3 infusion related reaction within 24 hours after the 1st FT538 infusion in any dose cohort or 1st enoblituzumab infusion in DC 5 or DC 6 and symptoms resolve to baseline within 12 hours.

If a patent experiences a Dose Limiting Toxicity (defined in next Section), enrollment moves directly to Stage 2 (CRM).

11.3.2 Dose Limiting Toxicity (All Patients)

All patients are monitored for dose limiting toxicity (DLT). DLT is defined as any treatment emergent toxicity at least possibly related to the study treatment meeting one of the following criteria based on CTCAE v5 within 28 days (14 days for ascites) of the 1st FT538 infusion (for Cohort 5 and 6, DLT assessment starts with enoblituzumab and continues for 28 days after 1st FT538):

- Grade 3 organ disorders (pulmonary, hepatic, renal, or neurologic) and lasting more than 72 hours
- Any non-hematologic Grade 4 or 5 toxicity
- Grade 4 neutrophil count decreased that persists at Day 28 despite use of growth factor support
- Grade 3 or greater abdominal pain lasting more than 4 consecutive days and not controlled by standard analgesics
- Grade 3 or greater ascites within 14 days after FT538 administration in patients who had no ascites or Grade 1 ascites at enrollment and is not attributable to disease progression

In addition to documenting the event in the study's CRF's, DLTs are to be documented on the Event Form found in OnCore per Masonic Cancer Center procedures within 24 hours of knowledge.

11.3.3 Excessive Toxicity (All Patients)

Stopping rules also are in place independent of dose escalation as detailed in Section 14.4.

- Stopping Rule for Excessive DLT as determined by the study statistician or designee

The following events must be reported within 24 hours of knowledge:

- **Grade 3 or greater Infusion Related Reaction** through Day 28 in association with any FT538 infusion in any Dose Cohort or in association with enoblituzumab in Dose Cohort 5 and 6.
- **Early Death** (Grade 5 Event) within 28 days after the last dose of FT538 (21 days after Dose 2 of enoblituzumab in Cohorts 5 and 6) and not attributable to disease progression. Any one death, suspends study enrollment per Section 14.4.

11.4 SAE Documentation

Any event meeting the definition of a serious adverse event (SAE) requires documentation using the MCC SAE Report Form in OnCore.

Deaths, including due to disease within 1 year after the 1st FT538 cell infusion will be recorded as an SAE. Deaths due to disease should be recorded as a Grade 5 “Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease).

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

11.5 Expedited Reporting Requirements

The following events require expedited reporting:

Report to:	Criteria for reporting:	Timeframe:	Form to Use:	Submission email address
Advarra	unanticipated problems involving risks to subjects or others; unanticipated adverse device effects; protocol violations that may affect the subjects' rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data; subject death; suspension of enrollment; or termination of the study	promptly and no later than 2 weeks (10 business days) from the time the investigator learns of the event	Refer to the Advarra IRB Handbook	Advarra via study specific CIRBI Link
UMN IRB	Refer to Submitting Updates in ETHOS – External IRB Study/Site			
FDA	Unexpected and fatal or unexpected and life threatening suspected adverse reaction	no later than 7 Calendar Days	University of Minnesota SAE Report	Submit to FDA as an amendment to IND with a copy to: Fate Therapeutics at safety@fatetherapeutics.com if Cohort 5 or 6 to MacroGenics saereports@MacroGenics.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		
	All other events per CFR 312.33	at time of annual report	IND annual report	As an amendment to the IND
Fate Therapeutics	Any event meeting the definition of a SAE	no later than 5 Calendar Days	University of Minnesota SAE Report	Fate Therapeutics at safety@fatetherapeutics.com
	Any event meeting the definition of a SUSAR	no later than 3 Calendar Days		
MacroGenics, Inc	For patients assigned to enoblituzumab (Cohort 5 or Cohort 6): all SAEs, regardless of causality or expectedness	within 7 calendar days of awareness	University of Minnesota SAE Report	saereports@MacroGenics.com

12 Investigational Product Description, Supply and Potential Toxicities

Refer to Appendix III for expected toxicities associated with the cyclophosphamide and fludarabine lymphodepletion.

12.1 Enoblituzumab

Enoblituzumab will be administered at a dose of 15 mg/kg, initially calculated based on the patient's actual weight prior to the 1st dose (baseline) measurement. Significant (≥ 10%) change in body weight from baseline should prompt recalculation of the dose. Patients with body mass index (BMI) greater than or equal to 30 kg/m2, the enoblituzumab dose will be calculated using ideal body weight (IBW).

Refer to the Pharmacy Manual for further instructions on allowable parameters for dose rounding of enoblituzumab.

12.1.1 Availability

For the purposes of this study, enoblituzumab will be provided by MacroGenics.

12.1.2 Dosage Forms and Strength

Enoblituzumab DP is a sterile, preservative-free clear to slightly opalescent, colorless to pale yellow or pale brown solution supplied at a protein concentration of 25 mg/mL in a single dose 20 mL vial containing 17 mL DP (425 mg/vial). Some visible, proteinaceous enoblituzumab particles may be present. The product is formulated in 0.95 mg/mL sodium acetate trihydrate, 0.18 mg/mL glacial acetic acid, 90 mg/mL sucrose, and 0.1 mg/mL polysorbate 80, pH 5.1, in Sterile Water for Injection, USP.

12.1.3 Storage

Enoblituzumab will be stored in the University of Minnesota Investigational Drug Services (IDS) Pharmacy. Enoblituzumab should be stored under refrigeration at 2°C–8°C (36°F–46°F). Enoblituzumab must not be frozen. Monitor temperature and document and report any excursions. Protect from light during storage. DO NOT SHAKE.

12.1.4 Preparation

The desired amount of enoblituzumab should be withdrawn from the vial(s) and diluted to the appropriate final concentration with 0.9% Sodium Chloride Injection USP (normal saline), according to the instructions provided in the Pharmacy Manual. A sterile, non-pyrogenic, low-protein binding polyethersulfone (PES) 0.2 micron in-line filter administration set must be used for IV administration of enoblituzumab. The infusion bag containing enoblituzumab should be gently inverted to mix the solution. The dose solution should be administered via IV infusion over 120 (± 15) minutes with a commercially available infusion pump.

Before administration, the parenteral drug product should be inspected visually. If foreign particulate matter or discoloration is noted, drug should not be administered.

12.1.5 Warnings and Precautions

Enoblituzumab is an Fc-optimized humanized mAb administered via IV infusion. Infusion of mAbs can result in hypersensitivity reactions and/or CRS, therefore, precautions should be observed during enoblituzumab administration.

Reactions that occur during or shortly following the infusion of monoclonal antibodies can be caused by various mechanisms, including acute anaphylactic

(IgE-mediated) or anaphylactoid reactions against the monoclonal antibody, and serum sickness (type III hypersensitivity). Another, type of infusion reaction that can sometimes be severe, is attributable to CRS. CRS is a disorder or collection of disorders characterized by fever, rigors, chills, arthralgia, cough, dizziness, fatigue, nausea, headache, diaphoresis, tachycardia, hypotension or hypertension, pruritus, rash including urticaria, shortness of breath, and bronchospasm caused by the release of cytokines from cells.

Infusion related reaction or cytokine release syndrome was reported in 48.5% of 373 patients in MacroGenics-sponsored clinical trials of enoblituzumab, with 42.1% of patients experiencing IRR/CRS that were mild to moderate in severity. Events of IRR/CRS ≥ Grade 3 in severity were seen in 6.4% (n=24) of patients. Two of these patients with a ≥ Grade 3 IRR/CRS event experienced an event of life-threatening IRR/CRS (1 received enoblituzumab in combination with ipilimumab and 1 received enoblituzumab in combination with pembrolizumab).

Patients treated with enoblituzumab should be pre-medicated as described in Section 7.2.1, monitored closely during the infusion and be advised of the potential to develop allergy-like symptoms.

Refer to the current Investigator's Brochure for additional information.

12.1.6 Potential Toxicities

As of April 2021, 349 adult patients had received enoblituzumab at doses up to 15.0 mg/kg, which is the dose used in this study.

So far, the most important safety risk that has been identified with enoblituzumab is infusion-related reaction (IRR), including reactions known as cytokine release syndrome (CRS). IRRs are effects due to a drug that may occur during or shortly after an infusion. Signs and symptoms of an infusion-related reaction may include fever, chills, nausea, vomiting, headache, muscle stiffness, rash, itching, low blood pressure, and difficulty breathing. IRRs can be life threatening and, in rare cases, may cause death. For all adult studies, IRRs (including CRS) have occurred in a 48% patients receiving treatment with enoblituzumab. Most of the infusion-related reactions observed in patients receiving enoblituzumab have been mild to moderate in severity with 6 % of patients having more severe infusion-related reactions (including two who experienced life-threatening IRR events). These patients, some of whom were hospitalized for these reactions, recovered after receiving treatment with steroids, antihistamines and intravenous fluids.

The following were the most common side effects that were considered related to enoblituzumab administration and were seen in at least 1 of 10 adult participants. These side effects have been generally mild or moderate.

- infusion related reactions (described above)
- fatigue
- nausea
- chills
- vomiting

Eleven (11) patients have experienced serious side effects that were considered related to enoblituzumab. Serious side effects that occurred in 3 or more patients included: IRRs.

Refer to the current Investigator's Brochure for additional information.

12.2 FT538

FT538 drug product comprises expanded allogeneic natural killer cells, derived from a clonal, CD38 knockout, human-induced pluripotent stem cell line, that expresses high-affinity, non-cleavable CD16 receptor (hnCD16) and interleukin (IL)-15/IL-15 receptor fusion protein (IL-15RF).

FT538 cells are suspended in infusion medium consisting of Plasma-Lyte A (pH 7.4) with albumin (human) and dimethyl sulfoxide. The drug product is not manufactured with antibiotics. The formulated drug product is aseptically filled into pre-sterilized, single-use cryopreservation bags with approximately:

• 2.8×10^6 viable cells (VC)/mL (total of 5×10^7 VC in an 18 mL/bag);

• 5.6×10^6 VC/mL (total of 1×10^8 VC in an 18 mL/bag); or

• 2.8×10^7 VC/mL (total of 5×10^8 VC in an 18 mL/bag).

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

12.2.1 Availability and Storage

FT538 is supplied by Fate Therapeutics for the purpose of this study in a pre-sterilized, single-use CryoStore™ 50 EVA, 10-30 mL freezing bag.

The cell product is delivered to and stored in the University of Minnesota Molecular Cellular Therapeutics (MCT) lab until needed for administration. At MCT the following occurs:

- Upon receipt of the VPLN shipper, open the outer lid and remove the packing slip.

- Check the contents of the shipper against the packing slip. The shipping documentation should remain on file with other IMP documentation at the clinical study site.
- Carefully open cassettes and confirm the product label against the packing slip. Visually inspect each FT538 bag to ensure it is not compromised in any manner and that there are no visible defects or leaks. Use care to conduct this inspection under temperature control to avoid temperature excursions.
- Confirm that the contents arrived frozen.
- Once the temperature monitoring data has been received, file it with the FATE Investigational Medicinal Product Accountability Log.

FT538 must be stored in the vapor phase of liquid nitrogen (VPLN) at ≤-150°C, in a temperature-monitored and alarmed VPLN 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. If the temperature warms to >-150°C up to -135°C for >10 minutes or >-135°C for any amount of time, Fate Therapeutics (FATE) must be notified.

12.2.2 Product Labeling

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

12.2.3 Route of Administration

The thaw procedure using a water bath or alternate equipment is set-up by MCT per established procedures and transferred to the place of administration.

FT538 must be administered using an IV administration set without an in line filter (filter is not required for IP administration). FT538 is administered as an IP infusion via gravity after any ascites or IP wash fluid has been drained per Section 7.4 into the previously placed IP catheter/peritoneal port as described in Section 7.1 using a pleurx peritoneal catheter kit and pleurx drainage kits manufactured by Becton Dickinson, Franklin Lakes, NJ. The catheter is Device Class 2 and is 510K-clearedK051711.

Administration of FT538 should be initiated as soon as practical after thawing, preferably within 20 minutes. Do not initiate infusion of drug product that has been thawed for more than 60 minutes. Infusion of all thawed product (including subsequent saline rinse of empty bag) must be completed within 90 minutes from

when the bag was first thawed. Refer to Section 7.4.2 for details of post infusion flush and distribution of the infusate within the abdominal cavity.

12.2.4 FT538 Product Resupply

Frequent meetings are held between the study team and Fate Therapeutics to review each study in with Fate products at the University of Minnesota. Included as a part of these meetings is a summary of product used, remaining FT538 bags, and upcoming product need.

12.2.5 Potential Risks Associated with FT538

In this study FT538 is infused by intraperitoneal (IP) infusion. In our previous studies of IP infusion of NK cell products including Fate NK100 and FT516 (each given with IL-2) abdominal pain and cramping once observed in the majority of patients. Most were CTCAE 5 Grade 1 or Grade 2, with an occasional Grade 3 event. The pain usually was managed with oral and/or intravenous analgesics.

Refer to Section 8 for potential toxicities associated with intravenous (IV) administration.

13 Study Data Collection and Monitoring

13.1 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. The production server is located in the UMN datacenter (WBOB).

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.

13.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRF) developed within the University of Minnesota OnCore based on its library of standardized forms. The e-CRFs will be approved by the study PI and the UMN 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-CRF based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

13.3 Data and Safety Monitoring Plan

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 can be accessed at https://z.umn.edu/dsmp.

For the purposes of data and safety monitoring, this study is classified as high risk (early in human, under locally sponsored IND). Therefore the following requirements will be fulfilled:

- At least quarterly review of the study's progress by the Masonic Cancer Center Data and Safety Monitoring Council (DSMC).
- 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 Sponsor (Dr. Geller) will submit a progress report annually. The report will be submitted within 60 days of the anniversary date that the IND went into effect.

13.4 Regular Team Meetings to Review Safety

Regular meetings will be held to facilitate communication regarding the study's progress in terms of individual patient safety including events meeting the definition of dose limiting toxicity, excessive toxicity (early study stopping rule), serious adverse events (SAEs) and overall impact on future enrollment.

At a minimum each patient is reviewed at the end 1st 28 days to document the DLT status and to confirm the timing and dose level for the next patient enrolled.

The outcome of these discussion will be documented in the meeting minutes and the statistician or designee will send out a confirmatory email summarizing the discussion which will become part of the regulatory record.

Other issues for discussion may include pending patients, patient updates, summary of safety reports, and case report form completion.

The study assigned CRC or designee is responsible for arranging these meetings and preparing the agenda. Meetings will occur every 2 weeks; however, these may be scheduled more or less frequently at the discretion of the PI and/or the CRC. The safety discussion may be part of the regular PI meeting but must be documented as above (in study minutes and post-meeting email from the statistician or designee).

Expected participation includes the Principal Investigator, the Study Statistician or designee and relevant CTO staff (CRC-RN, CRC, Regulatory Specialist, and Program Manager) or appropriate designee.

In the situation of a patient completing the DLT period between scheduled meetings, communication via email may be used in lieu of a meeting provided the patient was discussed at the prior meeting and will be included on the next meeting's agenda.

13.5 Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility until notified by the Masonic Cancer Center Clinical Trials Office that the study records may be destroyed.

14 Statistical Considerations

14.1 Study Design, Objectives and Endpoints

This Phase I study will test up to 7 dose strategies of FT538 to determine the maximum tolerated dose (MTD) of FT538 with a maximum enrollment of **33** patients.

There are 7 potential dose cohorts defined for this study. The trial will be conducted with no intra-patient escalation. The starting dose will be $1x10^8$ cells FT538 cells/dose with no enoblituzumab. The subsequent planned cohorts will be $3x10^8$ FT538 cells/dose with no enoblituzumab, $1x10^9$ FT538 cells/dose with no enoblituzumab, and then $1.5x10^9$ FT538 cells/dose with no enoblituzumab, unless a dose-limiting toxicity (DLT) occurs at Cohort 1, when continual reassessment method (CRM) stage is initiated. Dose escalation will continue in combination with enoblituzumab starting at one dose below the highest dose reached from the 1st five cohorts given that we reach at least Cohort 2 without enoblituzumab. This will potentially continue up through $1.5x10^9$ FT538 cells/dose + enoblituzumab. 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). A cohort of two patients will start at Cohort 1 with subsequent planned cohorts as described in Table 6:

Table 6. Infuse FT53 cell product at the assigned dose on Day 1, Day 8 and Day 15

Cohort	FT538 Dose IP (cells per dose)
-1#	Monotherapy: IP FT538 at 5 x 10^7 cells/dose on Day 1, 8, and 15
1 (start)	Monotherapy: IP FT538 at 1 x 10^8 cells/dose on Day 1, 8, and 15
2	Monotherapy: IP FT538 at 3 x 10^8 cells/dose on Day 1, 8, and 15
3	Monotherapy: IP FT538 at 1 x 10^9 cells/dose on Day 1, 8, and 15
4	Monotherapy: IP FT538 at 1.5 x 10^9 cells/dose on Day 1, 8, and 15
5	IP FT538 at the safe dose (MTD-1) from the 1st 4 dose cohorts on Day 1, Day 8, and Day 15 plus IV enoblituzumab on Day -6, Day 22, then every 3 weeks until PD
6	IP FT538 at the highest dose (MTD) from the 1st 4 dose cohorts on Day 1, Day 8, and Day 15 plus IV enoblituzumab on Day -6, Day 22, then every 3 weeks until PD

Dose -1 may only be tested in Stage 2

The Phase I trial will be conducted in two consecutive stages: Stage 1 Step 1 will enroll two patients with at least 14 days apart at consecutively increasing doses until either of the following pre-defined treatment emergent adverse events occurs within 28 days of the 1st dose of FT538:

- Grade 3 abdominal pain not attributable to cancer lasting more than 48 hours and not controlled by standard analgesics
- Grade 3 infusion reaction

At this point Stage 1, Step 2 is initiated and the cohort size will increase from 2 to 3 patients. At least 14 days must separate the 1st and 2nd patients in a 3 patient cohort and a minimum of 28 days separate each 3 patient cohort. Note: if a DLT occurs during Fast-track (Step 1), enrollment moves directly to Stage 2 and Step 2 is not used.

At the 1st dose-limiting toxicity (DLT, defined in Section 7.5) occurs, Stage 2 of the Phase I trial will be initiated. Skeleton estimates of the probability of DLT at each dose will be cited based on discussion between the statistician and the primary investigator that allow for attractive operating characteristics. At least 14 days must separate the 1st and 2nd patients in a 3 patient cohort and a minimum of 28 days separate each 3 patient cohort. A one-parameter model has been chosen to link the risk of a DLT to the dose, where the probability of toxicity at dose i is modeled as $p_i^{\exp(\alpha)}$ where pi is a constant and α is the parameter to be estimated. The goal

will be to identify one of the 7 dose level strategies corresponding to the desired maximum toxicity rate of ≤25%.

If the CRM is initiated, the CRM will continually update the toxicity at the end of 28 days after the 3rd patient in each cohort. Each new cohort of three patients will be sequentially assigned to the most appropriate dose based on the updated toxicity probabilities. The MTD will be identified by the minimum of the following criteria: (1) the total sample size of 33 is exhausted, (2) or 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.

14.2 Sample Size

A maximum of 33 patients will be enrolled. Based on the simulations from Table 7, this should be sufficient and safe to define the MTD.

Table 7. **Operating characteristics for Adaptive-CRM**

Cells/ dose	Expected DLT, Expected SAE[1,2]			Excessive DLT, Expected SAE[1,2]		
	True Probability	Prob. of dose[3]	N[4]	True Probability	Probability of dose	N
5 x 10^7 alone[+]	1%, 1%	0%	0	20%,10%	63%	18
1 x 10^8 alone*	1%, 2%	0%	2	25%,18%	0%	6
3 x 10^8 alone	3%, 5%	0%	2	35%, 29%	34%	6
1 x 10^9 alone	6%, 8%	0%	2	45%, 50%	3%	3
1.5 x 10^9 alone	7%, 10%	0%	3	50%, 60%	0%	0
Safe dose from 1st 3 levels (MTD-1) +enoblituzumab	8%, 12%	0%	3	60%, 66%	0%	0
Highest dose from 1st 3 levels (MTD) + enoblituzumab	10%, 15%	100%	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

* Starting dose

[+] Dose -1 may only be tested in stage 2.

Enrollment will most likely include 22 patients, or it could be as high as 33 patients if DLTs are encountered early. Accrual should range from 10-12 patients per year so study accrual is expected to be complete within 24-36 months.

Any patient who does not receive at least 1 dose of FT538 will be replaced to complete enrollment at a specified dose (e.g. 10 evaluable patients at the MTD).

14.3 Statistical Analysis

The primary objective of this trial is to identify the maximum tolerated dose (MTD) which will be determined per the study design and consultation with the study statistician using R prior to each cohort enrollment. Due to small patient numbers

at the MTD, estimation of toxicity rates, clinical activity of progression free survival (PFS) at 12 months will be estimated in a descriptive format using simple frequencies, proportions, means, standard deviations/standard errors, medians and ranges and respective plots. Potential censored data such as PFS and relapse/progression and NRM may be estimated by Kaplan-Meier curves at 12 months. Relapse/progression and NRM may be estimated by cumulative incidence, treating NRM and relapse as competing risks, respectively.

14.4 Monitoring Guidelines (Early Study Stopping Rules)

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

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 by the study statistician. The trial will be stopped if the posterior probability that the lowest dose is unacceptably toxic (> 25% of patients) is greater than 80%.

Grade 3 or greater Infusion Related Reaction through Day 28 in association with any FT538 infusion in any Dose Cohort or in association with enoblituzumab in Dose Cohort 5 and 6

The goal is to construct a boundary based on Grade 3 or greater 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 33. With these stipulations, the trial will be stopped and reviewed if 2/7, 3/16, 4/28 or 5 patients have events by Day 28. If the true probability of infusion related toxicity is 20%, there is an 89% chance of triggering the monitoring boundary.

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 (21 days after Dose 2 of enoblituzumab in Cohorts 5 and 6) and not attributable to disease progression.

15 Conduct of the Study

15.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be 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.

15.2 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, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

15.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

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Appendix I – GOG PS Scale and NYHA Classification

GOG Score	Activity Level
0	Fully active, unrestricted activities of daily living
1	Ambulatory, but restricted in strenuous activity
2	Ambulatory, and capable of self care. Unable to work. Out of bed for greater than 50% of waking hours
3	Limited self care, or confined to bed or chair 50% of waking hours. Needs special assistance
4	Completely disabled, and no self care
5	Dead

NYHA Class	Patients with Cardiac Disease (Description of HF Related Symptoms)
Class I (Mild)	Patients with cardiac disease but without resulting in limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation (rapid or pounding heart beat), dyspnea (shortness of breath), or anginal pain (chest pain).
Class II (Mild)	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain
Class III (Moderate)	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV (Severe)	Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

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Appendix II - Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference (CTEP)

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

  Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

  Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

  Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement –

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as *target lesions* and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as *non-target lesions* and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

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

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

https://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf

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 local prescribing information.

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
- • 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 local prescribing information.

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 – Management of Clinical Neurotoxicity

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 A-1, Table A-2, and Table A-3) and/or institutional practice.

Table A-1 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 A-2 • 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 A-3 • 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 A-2 • Stage ≥3 papilloedema, with a CSF opening pressure ≥20 mmHg or cerebral oedema, should be treated as per algorithm in Table A-3

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.

Table A-1 Recommendations for the Management of Encephalopathy Syndrome	
Grade	**Management**

Reference: Neelapu 2018.

Table A-2 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 A-3 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 A-1) • 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.