A Phase I Study of FT538, a First-of-Kind, Off-the-Shelf, Multiplexed Engineered, iPSC-Derived NK-Cell Therapy As Monotherapy in Relapsed/Refractory Acute Myelogenous Leukemia and in Combination with Daratumumab or Elotuzumab in Relapsed/Refractory Multiple Myeloma

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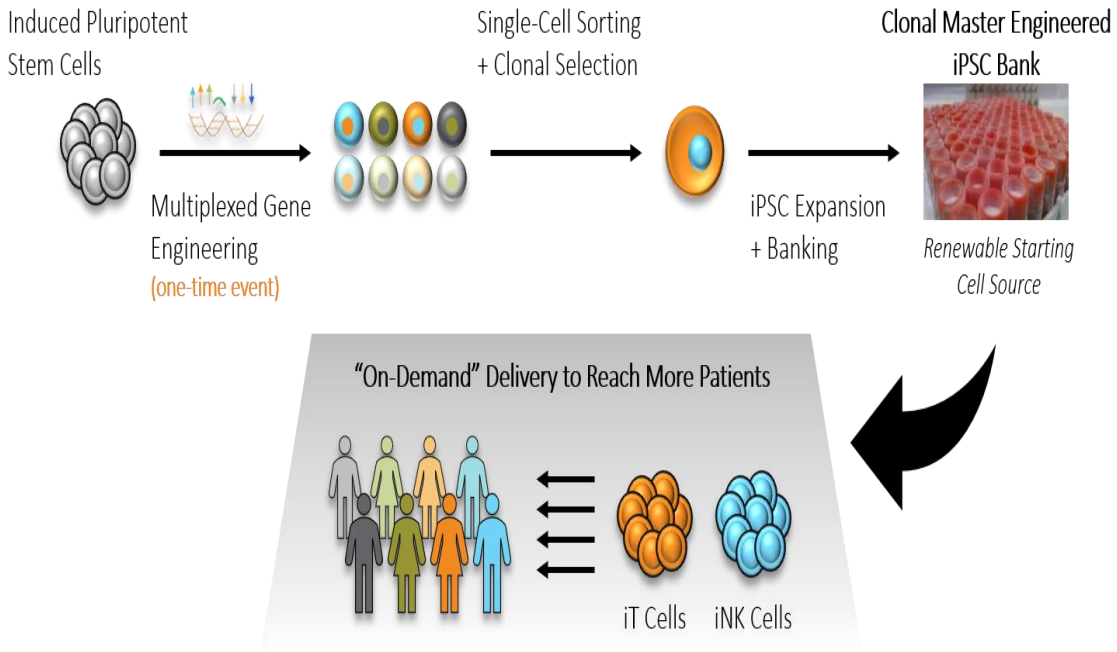
Background and iPSC Product Platform

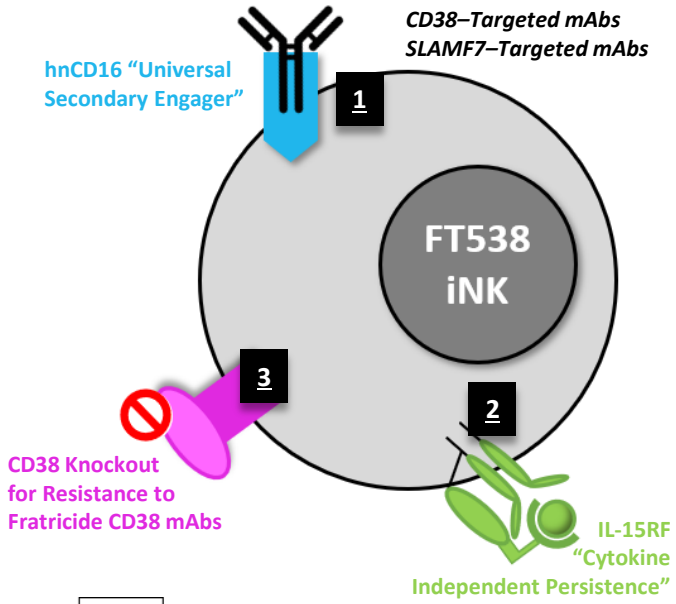
- Allogeneic natural killer (NK) cell therapies have been well tolerated, including absence of GvHD, cytokine release syndrome and neurotoxicity (Liu et al. 2020), with documented anti-tumor activity in patients with relapsed/refractory (r/r) acute myelogenous leukemia (AML) and multiple myeloma (MM) (Lupo et al. 2019).
- However, NK cells have limited in vivo expansion with a short half-life, and the potential for deeper and more durable anti-tumor response is limited, as with T-cell therapy, by manufacturing constraints and inability to administer more than a single dose of cellular therapy.
- The monoclonal antibodies (mAbs) daratumumab and elotuzumab are approved for the treatment of MM (Darzalex® USPI, Empliciti® USPI). Even though these antibodies have good clinical activity, eventually patients relapse with MM.
- Engagement of the Fc portion of the mAb with CD16 of NK cells promotes antibody-dependent cellular cytotoxicity (ADCC). But anti-CD38 mAbs such as daratumumab cause fratricide due to CD38 expression on endogenous NK cells (Casneuf et al. 2017).
- Hence, better clinical outcomes can be obtained by combining therapeutic mAbs with allogeneic NK cells designed to enhance ADCC, that are resistant to anti-CD38 mAb-mediated fratricide, and that can be consistently administered in multiple doses.

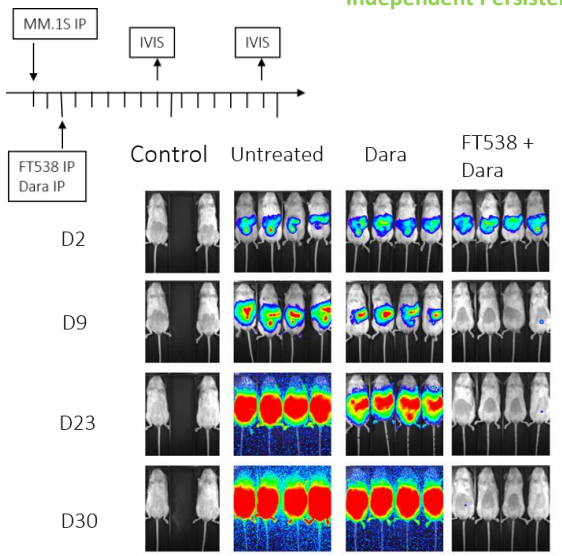


- A new, off-the-shelf, NK-cell platform utilizes a clonal, engineered, induced pluripotent stem cell (iPSC) line as starting material for the scaled production of NK cells through directed differentiation.
- This is unique because multiple cryopreserved doses consisting of uniformly engineered product can be generated for direct patient infusion in a cost-effective, off-the-shelf manner.

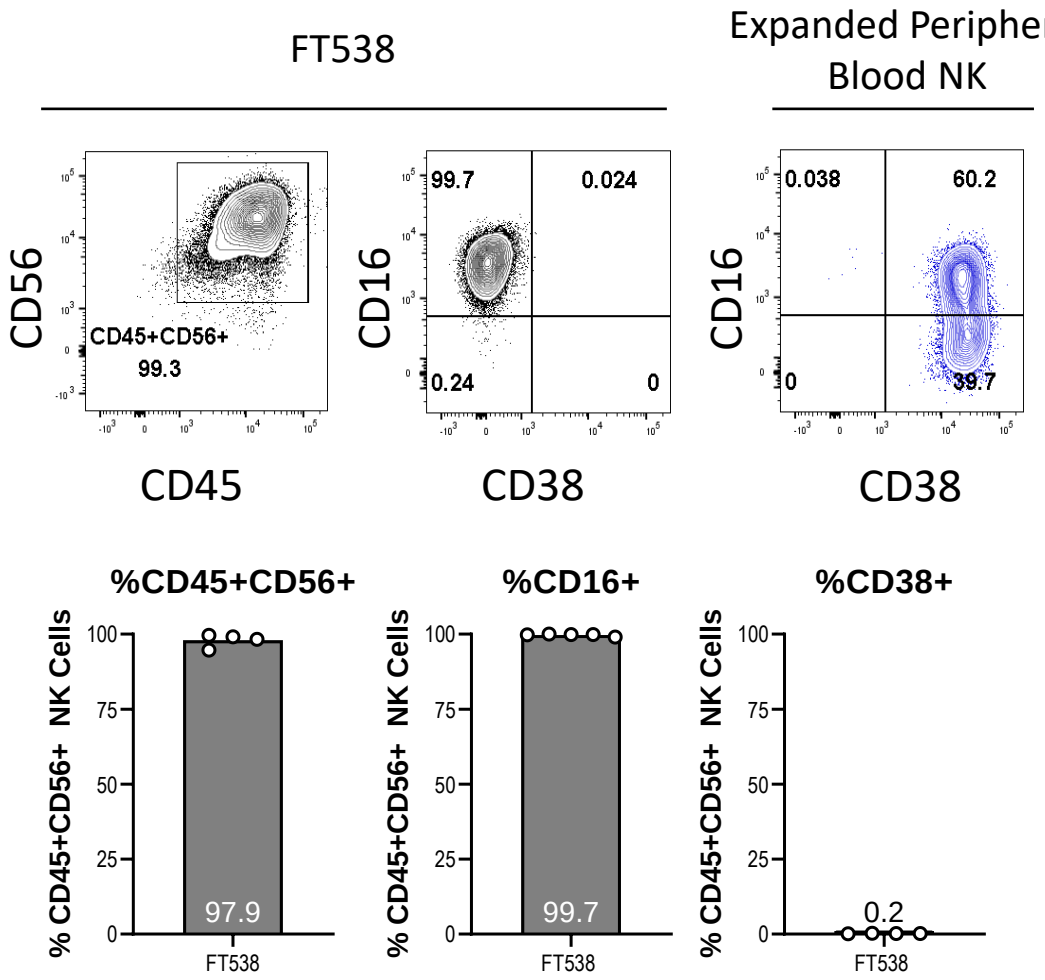
FT538, an iPSC-Derived, Multi-Engineered, NK-Cell Therapy

- FT538 is an investigational, multi-engineered, NK-cell therapy generated from a clonal master iPSC line that serves as a renewable source for the mass production of off-the-shelf NK cells.
- FT538 contains 3 engineered modalities for enhanced innate immunity:
    1. High-affinity 158V, non-cleavable CD16 Fc receptor for augmented ADCC
    2. Interleukin (IL)-15/IL-15 receptor fusion that promotes cytokine-autonomous persistence
    3. CD38 knockout to mitigate NK cell fratricide by CD38-directed mAbs





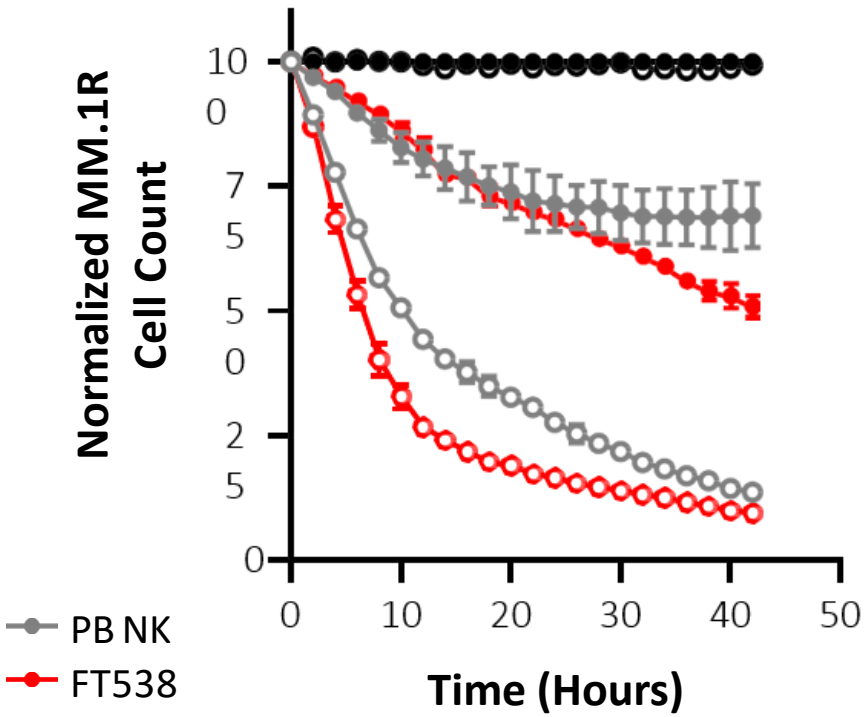
- An in vivo MM xenograft model demonstrated that the combination of FT538 + daratumumab led to enhanced ADCC and tumor control compared with daratumumab alone (Bjordahl et al. 2019).



- FT538 comprises a pure population of NK cells that are uniformly CD45+CD56+ and CD38-CD16+.
- FT538 is derived from a clonal iPSC master cell line, resulting in uniform CD38 knockout and hnCD16 expression on all cells.

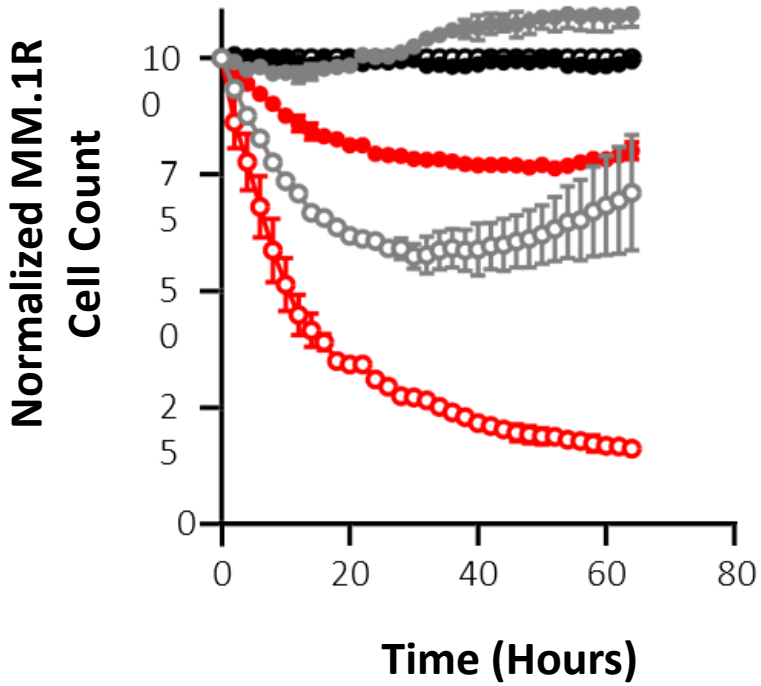
FT538 Demonstrates Enhanced Long-Term Killing in the Presence of Daratumumab in a Serial Stimulation Cytotoxicity Assay Compared to Peripheral Blood NK cells

MM.1R Killing
Round 1



Collect all effector cells and transfer to new MM.1R target cells

MM.1R Killing
Round 2

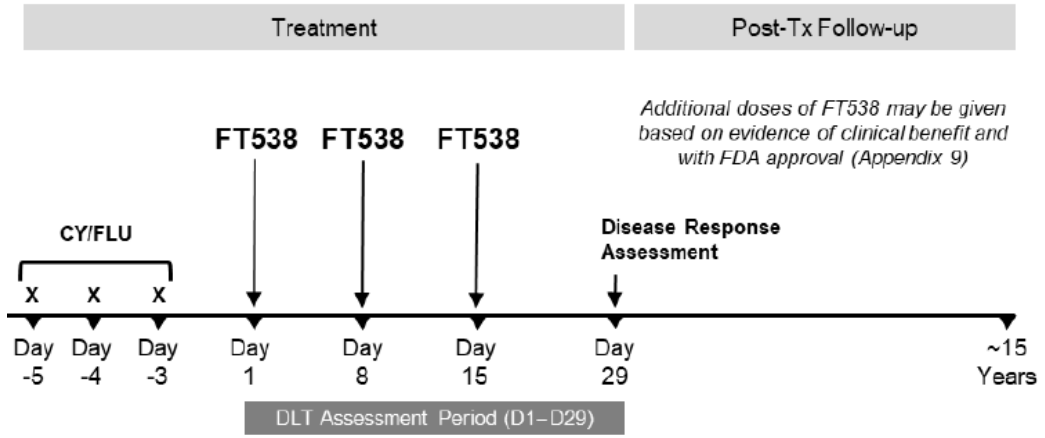


- FT538 maintains ADCC upon restimulation and outperforms peripheral blood NK cells.
- A combination of enhanced persistence due to IL-15RF and a lack of fratricide promotes enhanced, long-term ADCC when combined with daratumumab.

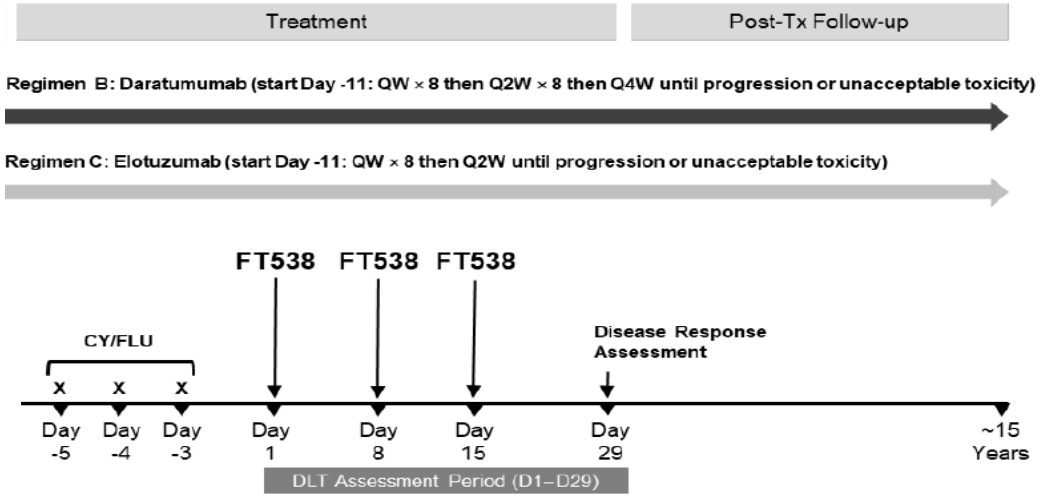
Bjordahl et al. 2019 and Cichocki et al. 2019

FT538-101: Study Design

Study Treatment Schema: Regimen A: r/r AML



Study Treatment Schema: Regimens B+C: r/r MM



Conditioning: Fludarabine (30 mg/m^2), cyclophosphamide (500 mg/m^2) x 3 days prior to FT538 infusion

3 + 3 Dose Escalation and Expansion

Regimen A: r/r AML FT538 Monotherapy	Escalation (1^8 -1.5^9 cells)	Expansion (n=15)
Regimen B: r/r MM FT538 + Daratumumab	Escalation (1^8 -1.5^9 cells)	Expansion (n=15)
Regimen C: r/r MM FT538 + Elotuzumab	Escalation (1^8 -1.5^9 cells)	Expansion (n=15)

Subjects may be eligible for retreatment of additional cycle(s) of FT538 based upon:

- Not experiencing any dose-limiting toxicity (DLT) and adequate resolution of adverse events related to study treatment(s)
- Evidence of ongoing clinical benefit and absence of signs and symptoms of progressive disease and/or decline in ECOG Performance Status
- May also be eligible if achieved objective response to FT538 but subsequently progressed or relapsed without receiving intervening anti-cancer therapy

FT538-101: Patient Population

Key Inclusion

Regimen A

- **Primary refractory AML**
  - De novo AML: Complete response (CR) not achieved after ≥2 inductions (if >60 years old, ≥1 induction required)
  - Secondary AML: CR not achieved after ≥1 induction
- **Relapsed AML**
  - Relapse after ≥1 re-inductions (if >60 years old, prior re-induction not required)

Regimens B and C

- **r/r MM**
  - Regimen B: Relapse or progression after ≥2 lines of prior therapy, including proteasome inhibitor (PI) and immunomodulatory drug (IMiD)
  - Regimen C: Relapse or progression after PI, IMiD, and anti-CD38 therapy
  - Measurable disease

Key Exclusion

Regimen A

- **r/r AML**
  - Diagnosis of promyelocytic leukemia with t(15;17) translocation

Regimens B and C

- **r/r MM**
  - ANC <1000/μL (no growth factor support ≤7 days prior)
  - Platelet count <75,000/μL (no platelet transfusion ≤72 hours prior)
  - Plasma cell count >2000/mm^3

All Regimens

- **r/r AML and r/r MM**
  - ECOG Performance Status ≥2
  - Inadequate organ function
  - Known CNS involvement
  - Prior allogeneic HSCT or allogeneic CAR T ≤6 months of first dose

FT538-101: Objectives and Endpoints

Objectives

Primary

- To determine the recommended Phase II dose (RP2D) for FT538 monotherapy in r/r AML
- To determine the RP2D for FT538 ± daratumumab or elotuzumab in r/r MM

Secondary

- Safety and tolerability of FT538 ± daratumumab or elotuzumab
- Anti-tumor activity of FT538 ± daratumumab or elotuzumab
- Pharmacokinetics (PK) of FT538 ± daratumumab or elotuzumab

Exploratory

- Association of PK/pharmacodynamics (PD) with safety and anti-tumor activity of FT538 ± daratumumab or elotuzumab
- Association of baseline clinical/tumor characteristics with safety and response endpoints following FT538 ± daratumumab or elotuzumab

Endpoints

Primary

- Incidence and nature of dose limiting toxicities (DLTs) to determine maximum tolerated dose or maximum administered dose
- RP2D based on overall safety and anti-tumor activity

Secondary

- Incidence, nature, and severity of adverse events
- Objective response rate by investigator per 2017 ELN criteria for r/r AML and per 2016 IMWG criteria for r/r MM
- Progression-free survival/event-free survival, relapse-free survival, overall survival, and/or duration of response by the investigator
- Determination of PK of FT538 in peripheral blood

Exploratory

- Detection of FT538 in bone marrow and/or tumor samples
- PD of FT538 as assessed by peripheral blood cytokines, immunophenotyping, and cellular function
- Assessment of tumor microenvironment in bone marrow and/or tumor samples pre- and post-treatment
- Proportion of subjects who achieve CR_{MRD-}

FT538-101: Initial Site Activation (up to 8 planned)

- Projected enrollment: Up to 105 subjects
- ClinicalTrials.gov Identifier: NCT04614636