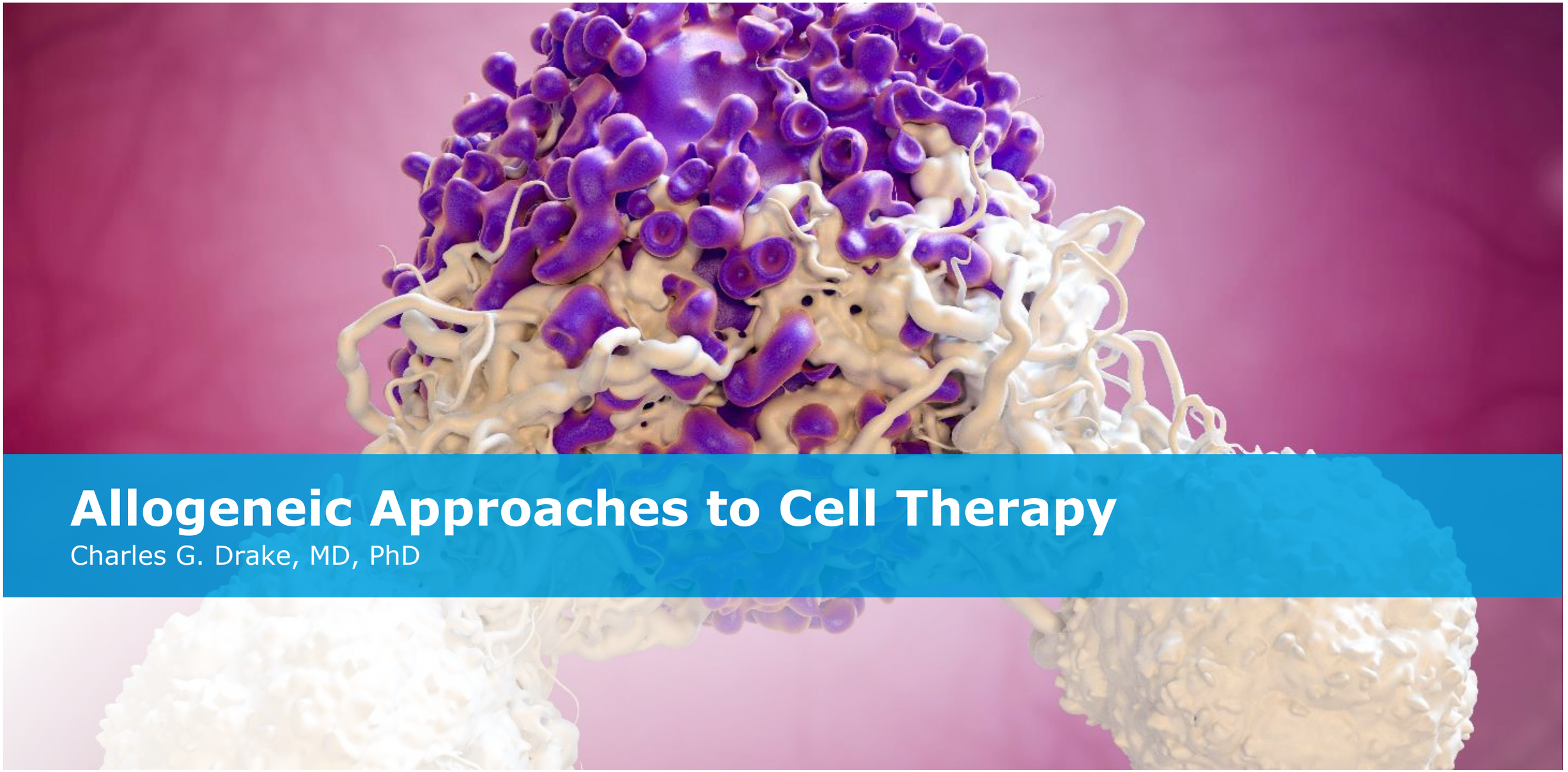

Allogeneic Approaches to Cell Therapy

Charles G. Drake, MD, PhD

Disclosure Information

Charles G. Drake

I am now an employee of Janssen Research and Development.

I will discuss investigational agents (but not off-label use) in my presentation.

I am a co-inventor on a patent concerning LAG-3, licensed from Johns Hopkins University to Bristol Myers Squibb, with associated royalties.

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2021 ASCO® ANNUAL MEETING

An Evolving Case of CAR-T Envy!

CILTACABTAGENE AUTOLEUCEL, A B-CELL MATURATION ANTIGEN–DIRECTED CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY, IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: UPDATED RESULTS FROM CARTITUDE-1

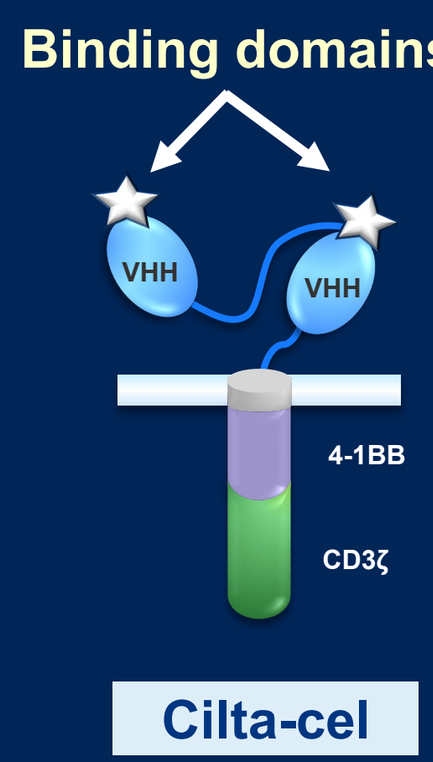
Saad Z Usmani[1], Jesus G Berdeja[2], Deepu Madduri[3], Andrzej Jakubowiak[4], Mounzer Agha[5], Adam D Cohen[6], Parameswaran Hari[7], Tzu-Min Yeh[8], Yunsi Olyslager[9], Arnob Banerjee[10], Carolyn C Jackson[8], Alicia Allred[10], Enrique Zudaire[10], William Deraedt[9], Xiaoling Wu[11], Marlene J Carrasco-Alfonso[11], Muhammad Akram[11], Yi Lin[12], Thomas Martin[13], Sundar Jagannath[3]

[1]Levine Cancer Institute-Atrium Health, Charlotte, NC, USA; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]Mount Sinai Medical Center, New York, NY, USA; [4]University of Chicago, Chicago, IL, USA; [5]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [6]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [7]Medical College of Wisconsin, Milwaukee, WI, USA; [8]Janssen R&D, Raritan, NJ, USA; [9]Janssen R&D, Beerse, Belgium; [10]Janssen R&D, Spring House, PA, USA; [11]Legend Biotech USA, Inc, Piscataway, NJ, USA; [12]Mayo Clinic, Rochester, MN, USA; [13]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

June 8, 2021

CARTITUDE-1: Introduction

- CARTITUDE-1 (NCT03548207) is a phase 1b/2 study evaluating cilta-cel, a CAR T-cell therapy with two BCMA–targeting single-domain antibodies, in patients with R/R MM who have been heavily pretreated[1]
  - At a median follow-up of 12.4 months after cilta-cel treatment, the overall response rate was 97% with an sCR rate of 67%; overall 12-month PFS and OS rates were 77% and 89%, respectively
- Here, we present updated results from CARTITUDE-1 in patients with a longer follow-up (median: 18 months)



BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; OS, overall survival; PFS, progression-free survival; R/R MM, relapsed refractory multiple myeloma; sCR, stringent complete response; VHH, variable heavy chain.

1. Madduri D, et al. *Blood* 2020;136(Suppl 1):22–25.

CARTITUDE-1: Phase 1b/2 Study Design

Primary Objectives

- Phase 1b: Characterize cilta-cel safety and confirm the recommended phase 2 dose
- Phase 2: Evaluate cilta-cel efficacy

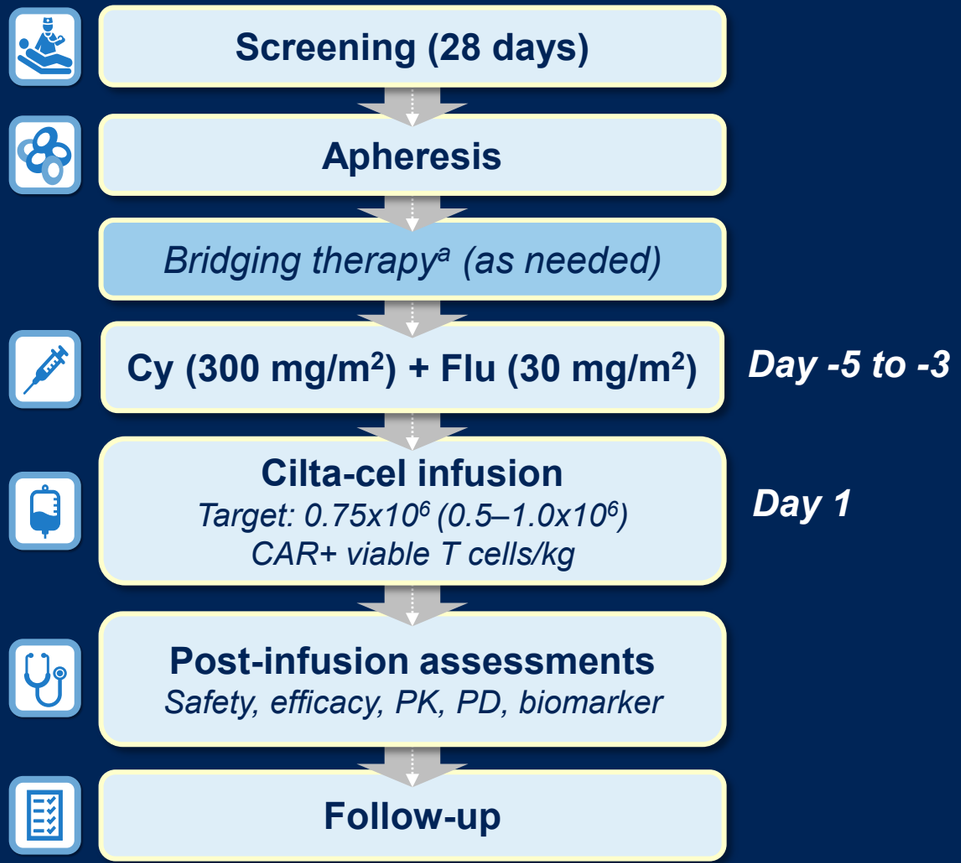
Key Eligibility Criteria

- Progressive MM per IMWG criteria
- ≥3 prior therapies or double refractory
- Prior PI, IMiD, anti-CD38 therapy
- Measurable disease
- ECOG PS ≤1

Median administered dose:

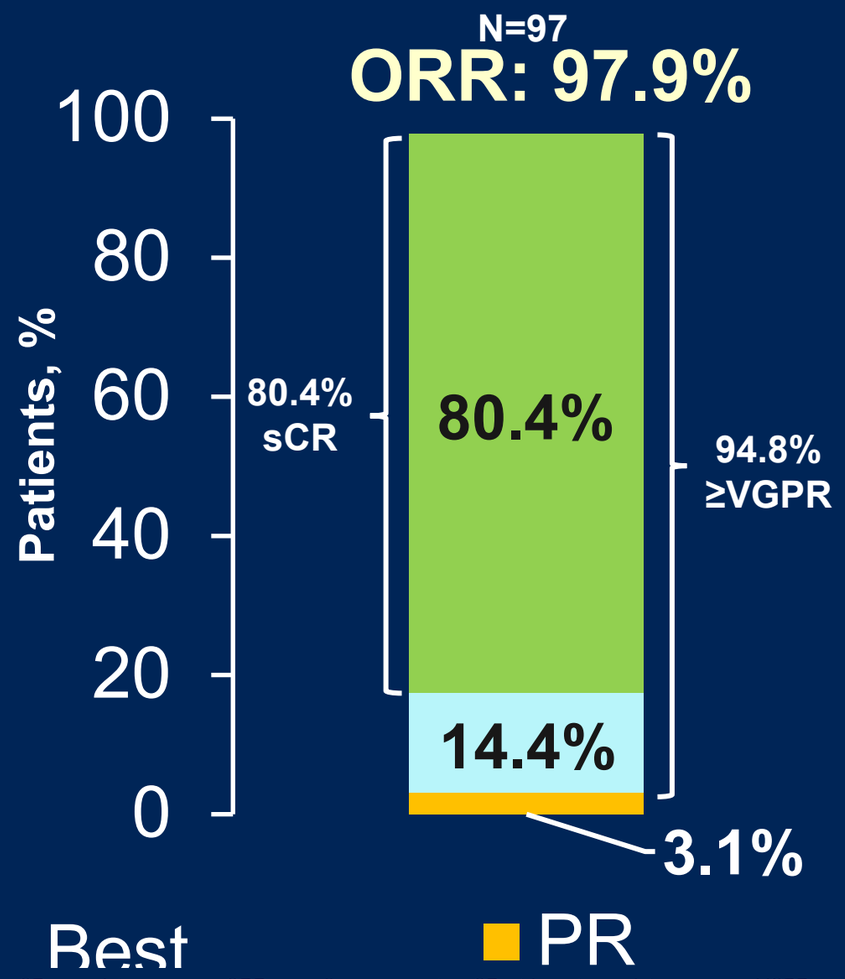
$0.71x10^6$ ($0.51–0.95x10^6$) CAR+ viable T cells/kg

For 80 kg pt ≈ 50 Million CAR-T Cells



CAR, chimeric antigen receptor; Cy, cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; Flu, fludarabine; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; PD, pharmacodynamics; PI, proteasome inhibitor; PK, pharmacokinetics. Feb 11, 2021 data cut-off. [a]Treatment with previously used agent resulting in at least stable disease.

CARTITUDE-1: Overall Response Rate

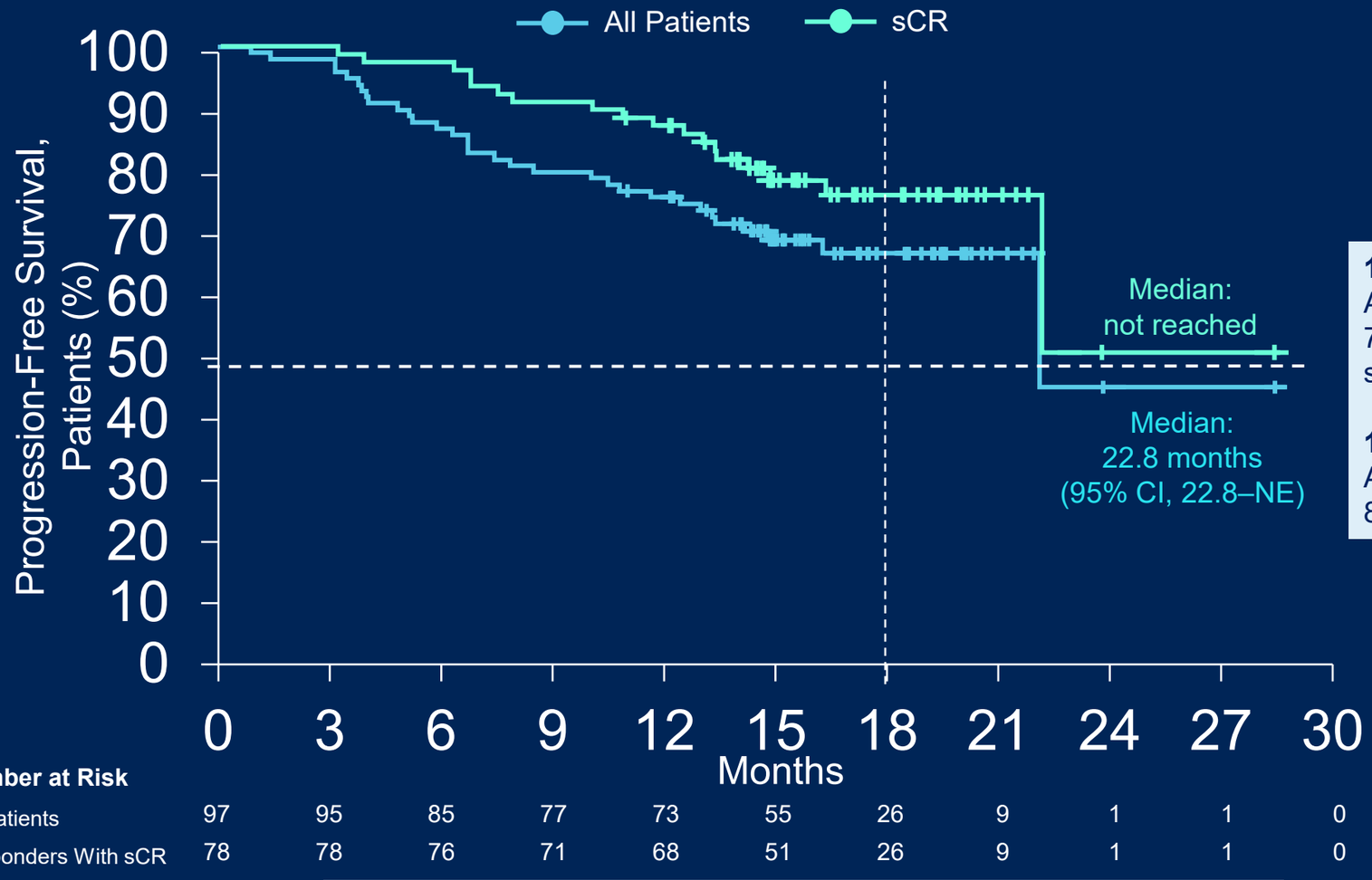


With longer follow-up, responses deepened with increasing rate of sCR

- Median time to first response: **1 month** (range, 0.9–10.7)
- Median time to best response: **2.6 months** (range, 0.9–15.2)
- Median time to ≥CR: 2.6 months (range, 0.9–15.2)
- Median duration of response: 21.8 months (95% CI, 21.8–NE)
  - Estimated 73% of responders have NOT progressed or died at 12 months
  - Median duration of response not reached in patients with sCR
- Response rates were comparable (range, 95–100%) across different subgroups (eg, number of prior lines of therapy, refractoriness, extramedullary plasmacytomas, and cytogenetic risk)[a]

CR, complete response; ORR, overall response rate; sCR, stringent complete response; VGPR, very good partial response. ORR assessed by independent review committee. [a]Subgroups by number of prior lines of therapy (≤4, >4), refractoriness (triple-class, penta-drug), cytogenetic risk (high risk, standard risk), baseline bone marrow plasma cells (≤30%, >30 to <60%, ≥60%), baseline tumor BCMA expression (≥median, <median), and baseline plasmacytomas (including extramedullary and bone-based).

CARTITUDE-1: Progression-Free Survival



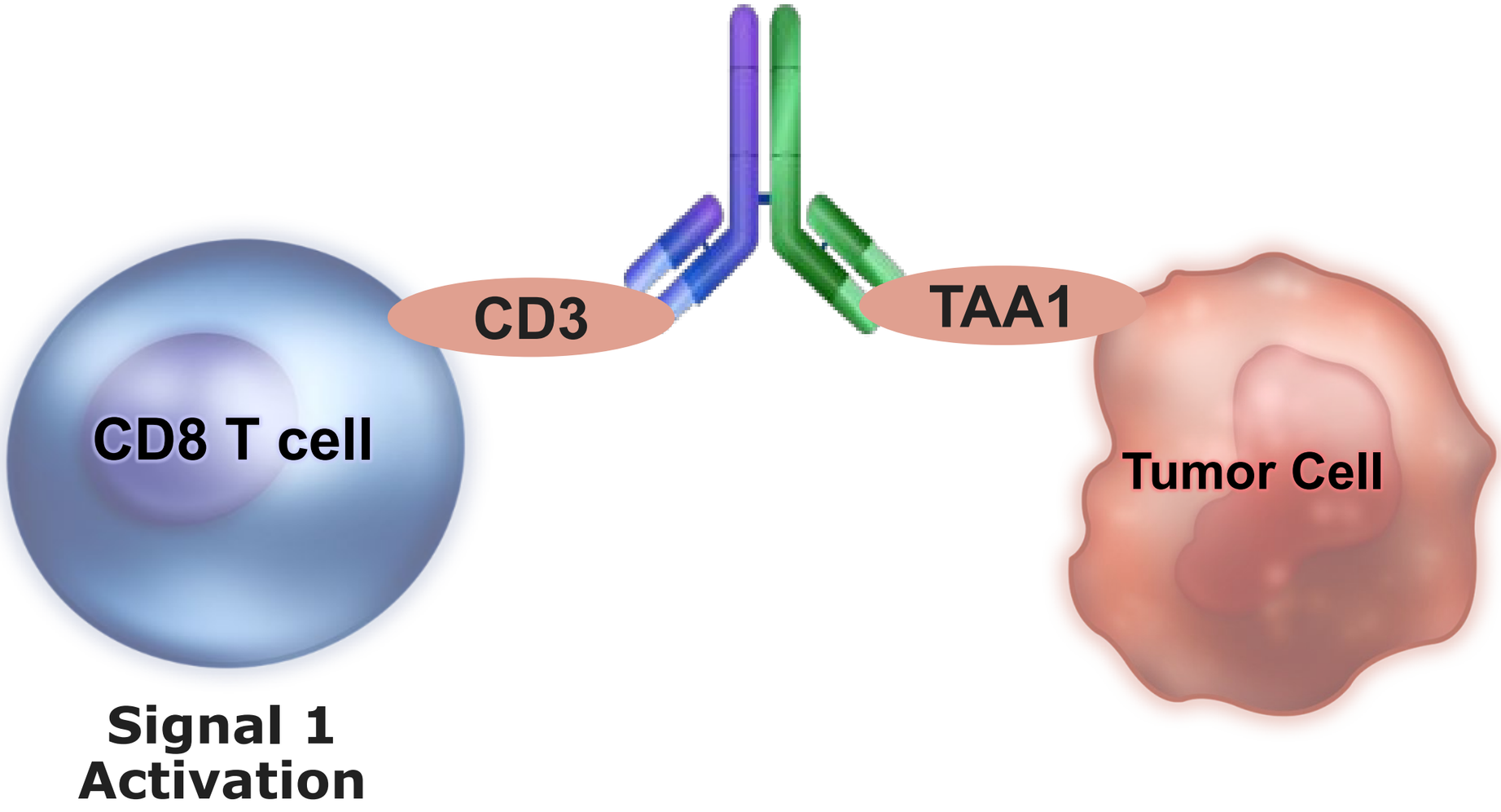
18-month PFS
All Patients: 66.0% (95% CI, 54.9–75.0)
sCR: 75.9% (95% CI, 63.6–84.5)

18-month OS
All patients: 80.9% (95% CI, 71.4–87.6)

Median duration of follow-up: 18 months (range, 1.5–30.5)

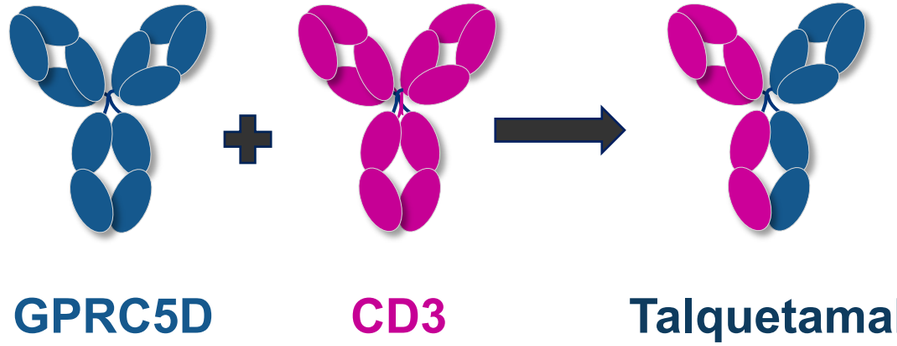
NE, not estimable; PFS, progression-free survival; OS, overall survival; sCR, stringent complete response.

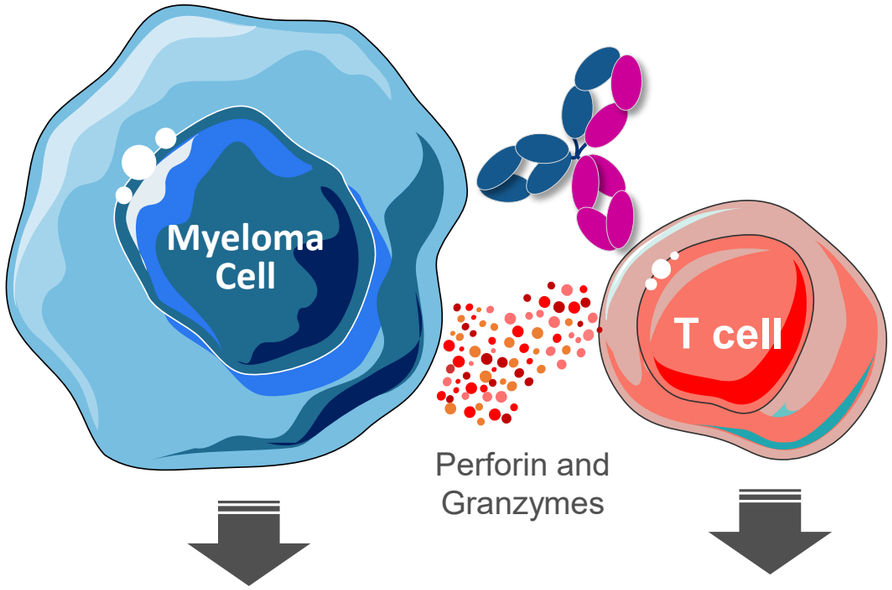
T-Cell Redirectors



Talquetamab: GPRC5D x CD3 Bispecific Antibody

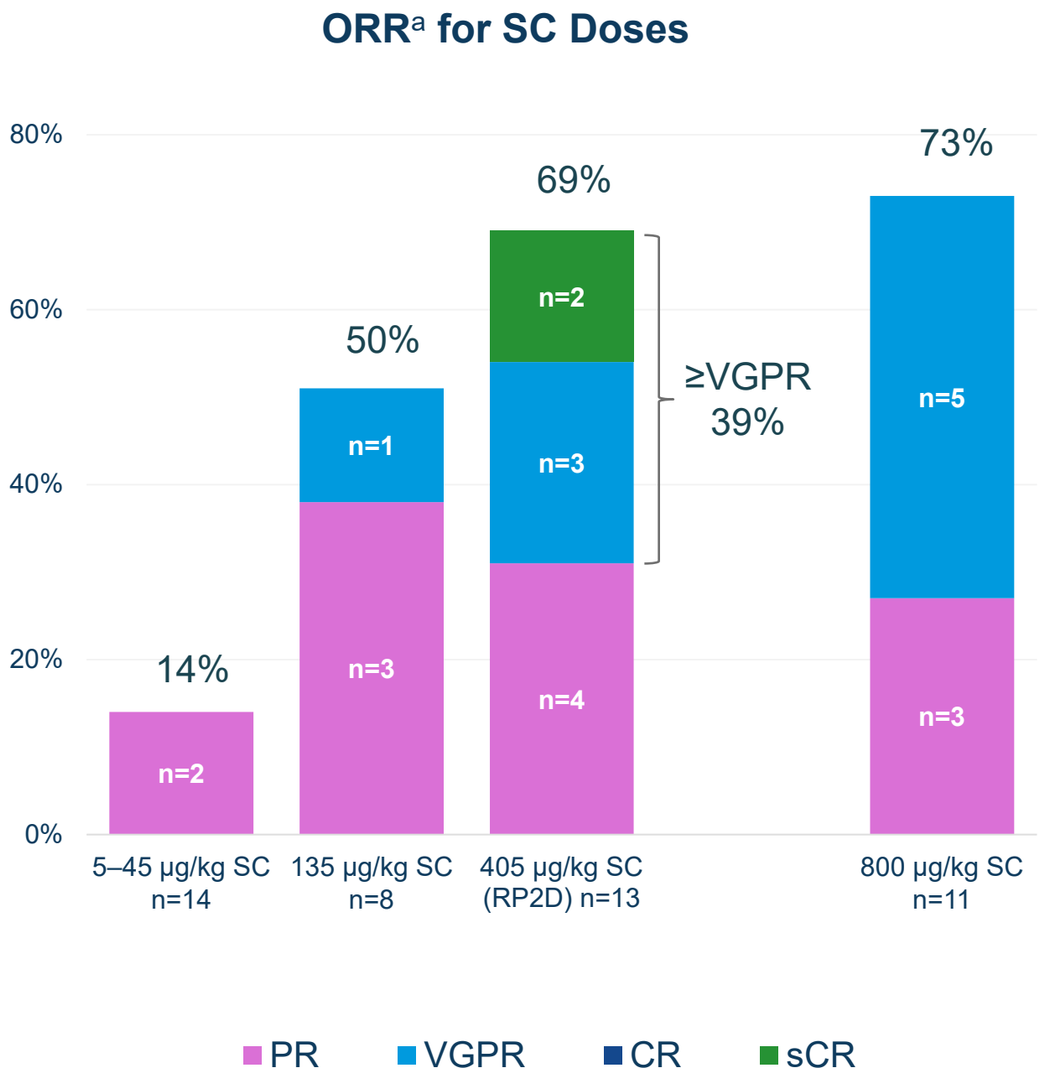
- Talquetamab is a first-in-class DuoBody® IgG4 PAA antibody that binds to both GPRC5D and CD3
- Talquetamab redirects T cells to GPRC5D-expressing myeloma cells to mediate cell killing
- Antitumor activity was demonstrated in primary myeloma cells and xenograft models of MM[1-3]
- Talquetamab's pharmacokinetic profile presents an opportunity for less frequent SC dosing
- First-in-human phase 1 study is ongoing to evaluate talquetamab in patients with RRMM (NCT03399799)





Talquetamab includes technology licensed from GenMab. [1]Smith *Sci Transl Med* 11(485):eaau7746. [2]Verkleij *HemaSphere* 3(S1):230, Poster #PF556.
[3]Pillarisetti *Blood* 135(15):1232. Ig, immunoglobulin; PAA, proline, alanine, alanine; RRMM, relapsed and/or refractory multiple myeloma

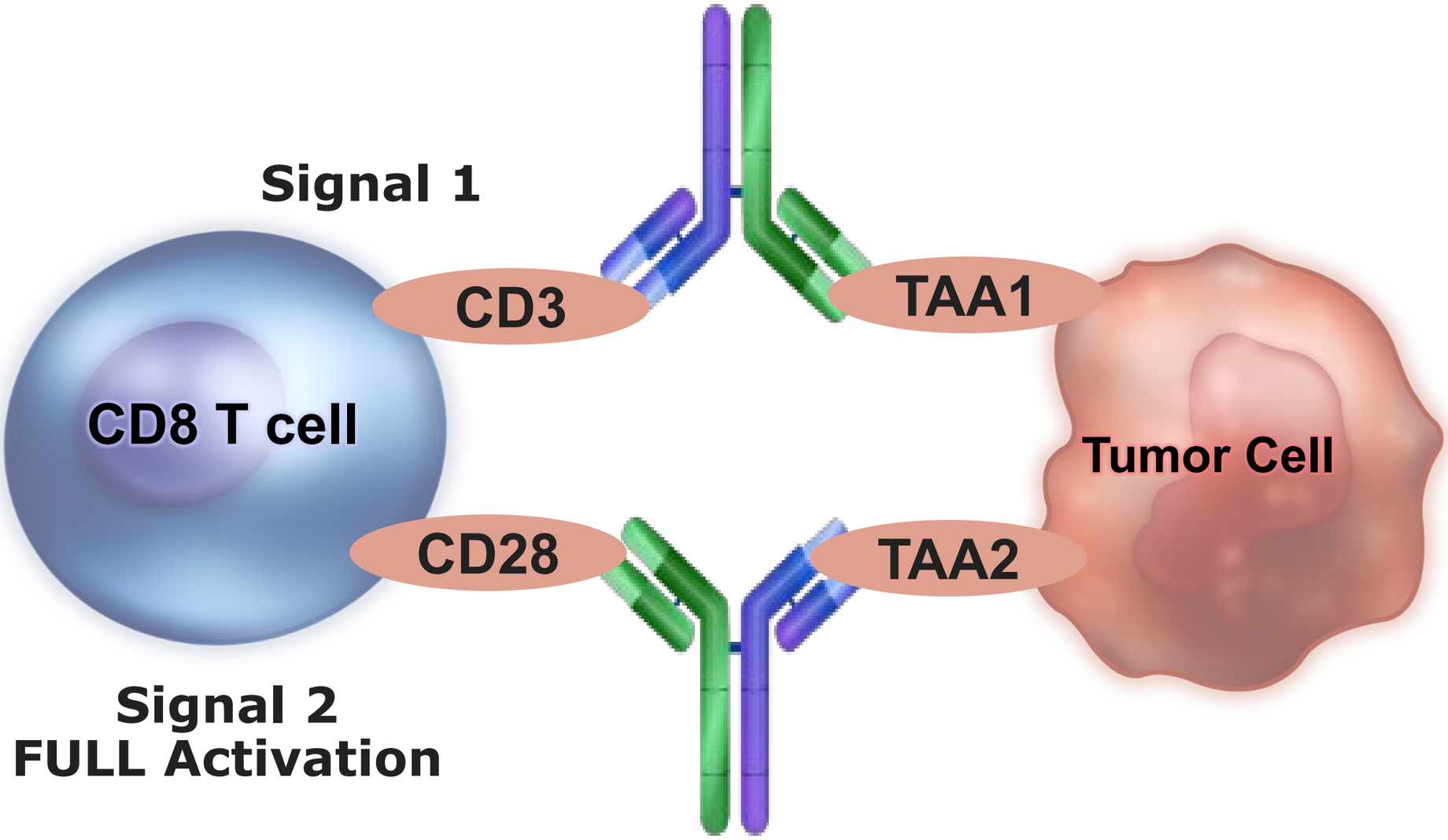
Talquetamab: Reasonable Activity for an Off-the-shelf Product



- **At the RP2D of 405 µg/kg SC**
  - 69% ORR (9/13)
  - Median 3.7-month (1.7–6.5) follow-up for responders
  - Median time to first confirmed response was 1 month (1–2)
  - 67% (6/9) of triple-class refractory patients responded
  - 100% (2/2) of penta-drug refractory patients responded
- **At most active doses of 20–180 µg/kg IV and 135–800 µg/kg SC**
  - 66% ORR (33/50)
  - ≥VGPR was 42%
  - 67% ORR (12/18) in IV cohorts and 66% ORR[a] (21/32) in SC cohorts

[a]Among response-evaluable patients who had at least 1 study treatment and 1 postbaseline disease evaluation; includes unconfirmed responses. CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response, VGPR, very good partial response

Next Generation T Cell Redirection



Next-Generation Cell Therapy

FIERCE Biotech

Biotech

J&J inks Fate deal to move into allogeneic CAR therapies

by Nick Paul Taylor | Apr 3, 2020 8:40am

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Autologous CAR-T

- Heterogenous product
- Logistical issues
- High COGS

vs

Allogeneic CAR-X (ipsc derived)

- Clonal/uniform product—from a master cell bank
- Precision engineering
- Targetable with CAR and/or mAb
- Lower COGs

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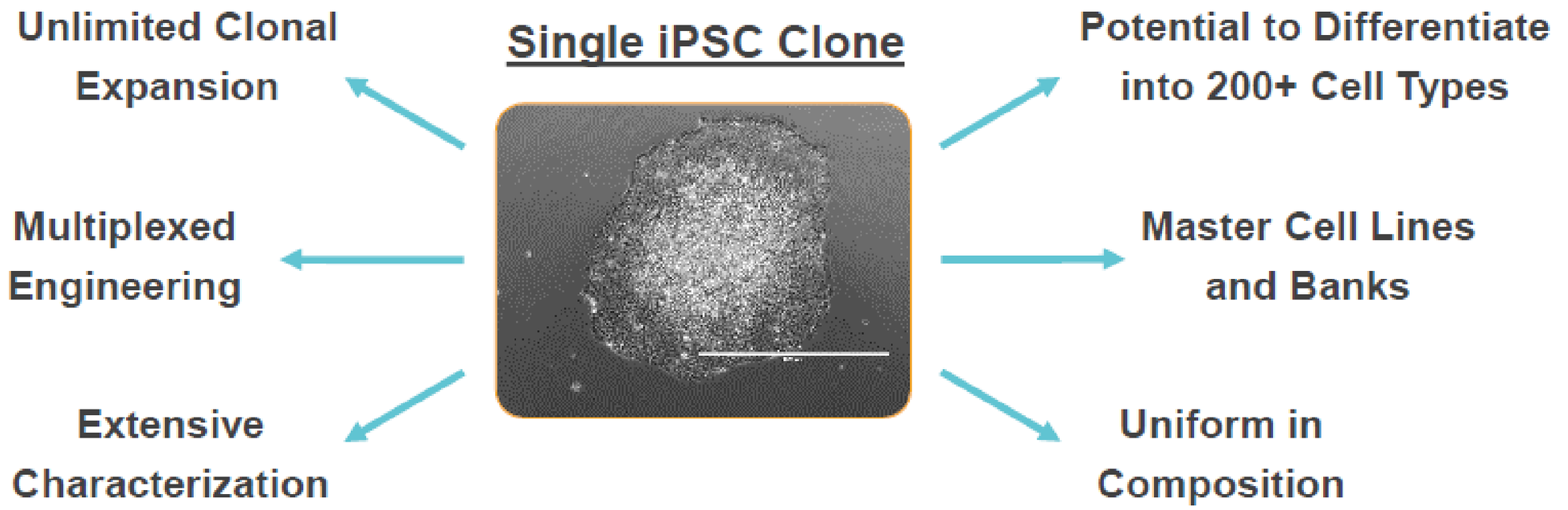
A Single Human Induced Pluripotent Stem Cell (iPSC)

A renewable source for making cell products



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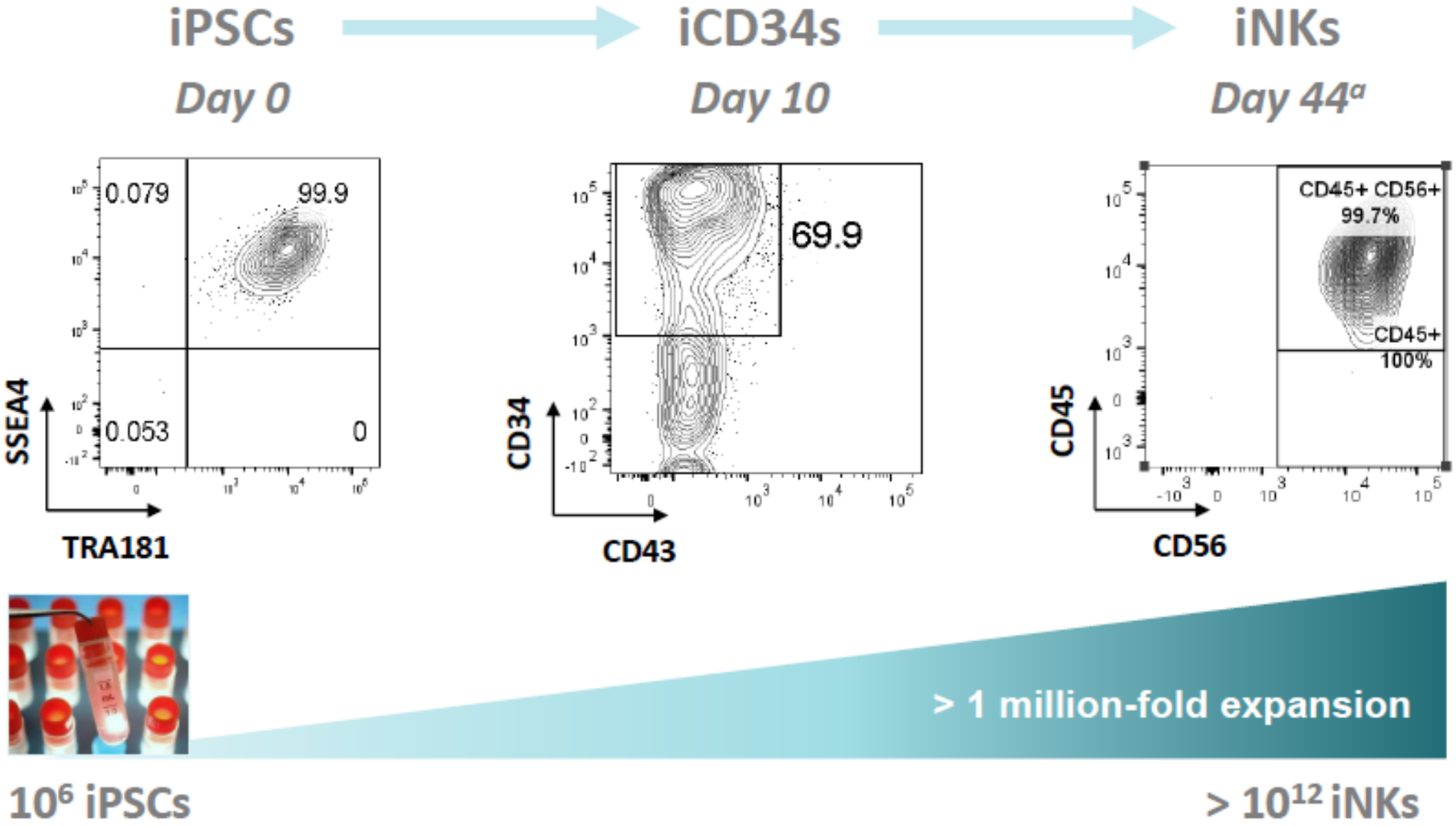
From iPSC to Natural Killer Cells (ipsc derived NK's)



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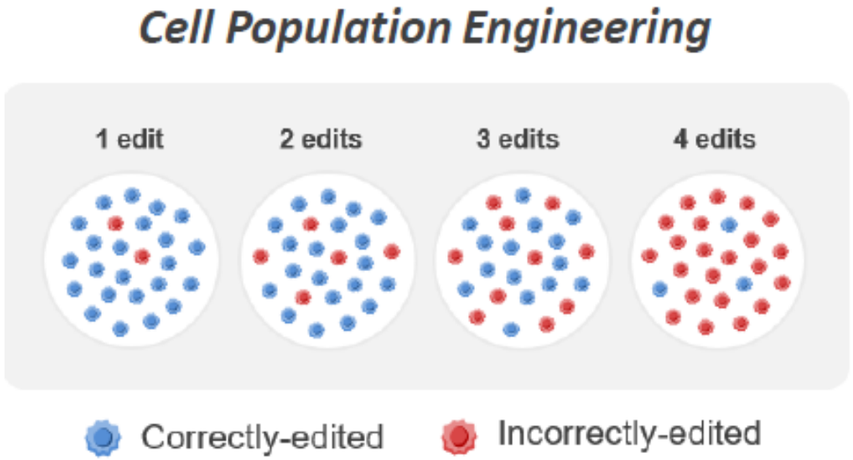
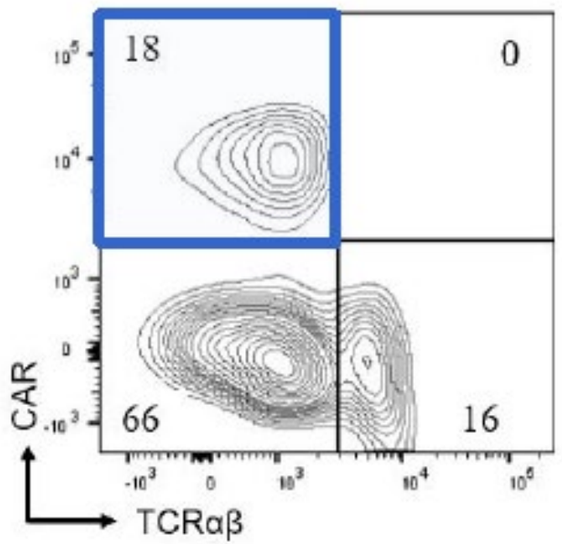
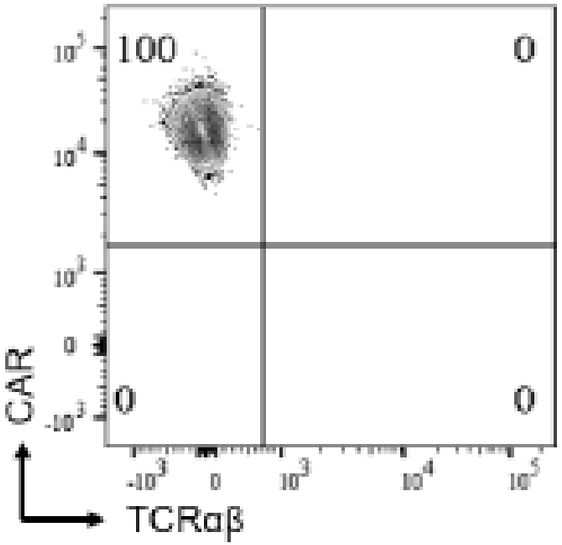
Some Gene Editing (Engineering) In The Process





Single cell ipsc isolation, characterization and selection



<u>Clonal</u> Master Cell Line

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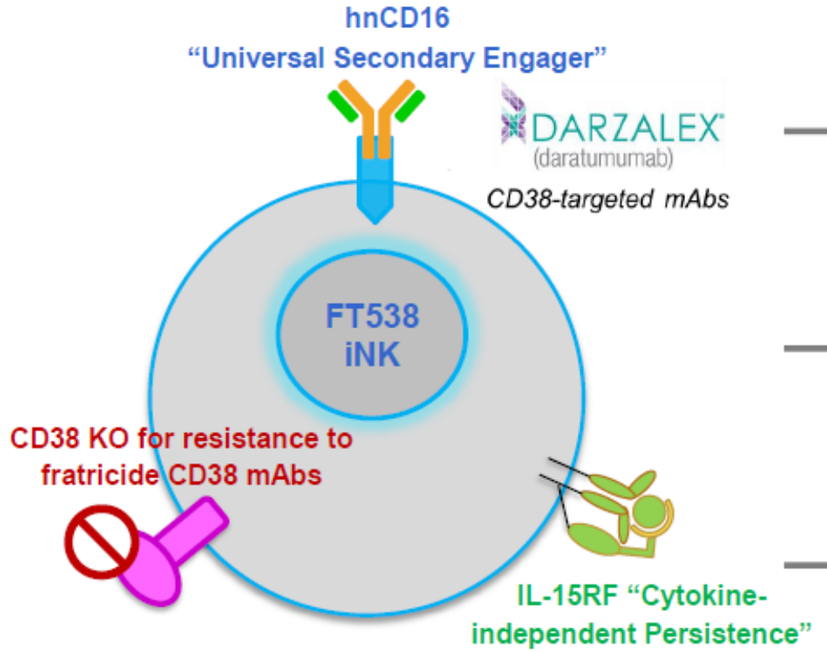
Three Edits

FT538: hnCD16 + IL-15RF + CD38KO NK Cell Product Candidate

First-ever CRISPR-edited iPSC-derived Cell Therapy

Engineered with Three Components to Enhance Multiple Mechanisms of Innate Immunity



hnCD16: High-affinity 158V, non-cleavable CD16 Fc receptor that has been modified to augment antibody-dependent cellular cytotoxicity by preventing CD16 down-regulation and enhancing CD16 binding to tumor-targeting antibodies

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CD38KO: Deletion of CD38 to eliminate anti-CD38 antibody mediated NK cell fratricide. Also shown to improve NK cell biology and potency through optimization of metabolic signaling

---

IL-15RF: Interleukin-15 receptor fusion, a potent cytokine complex that promotes survival, proliferation and trans-activation of NK cells and CD8 T cells

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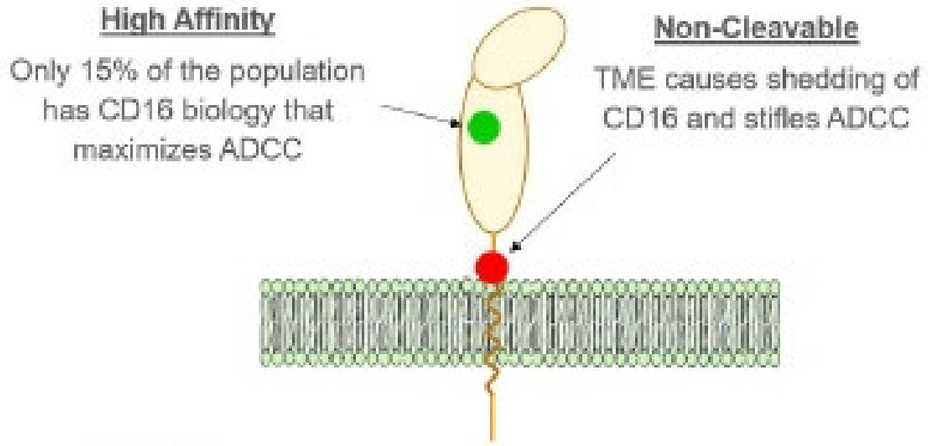
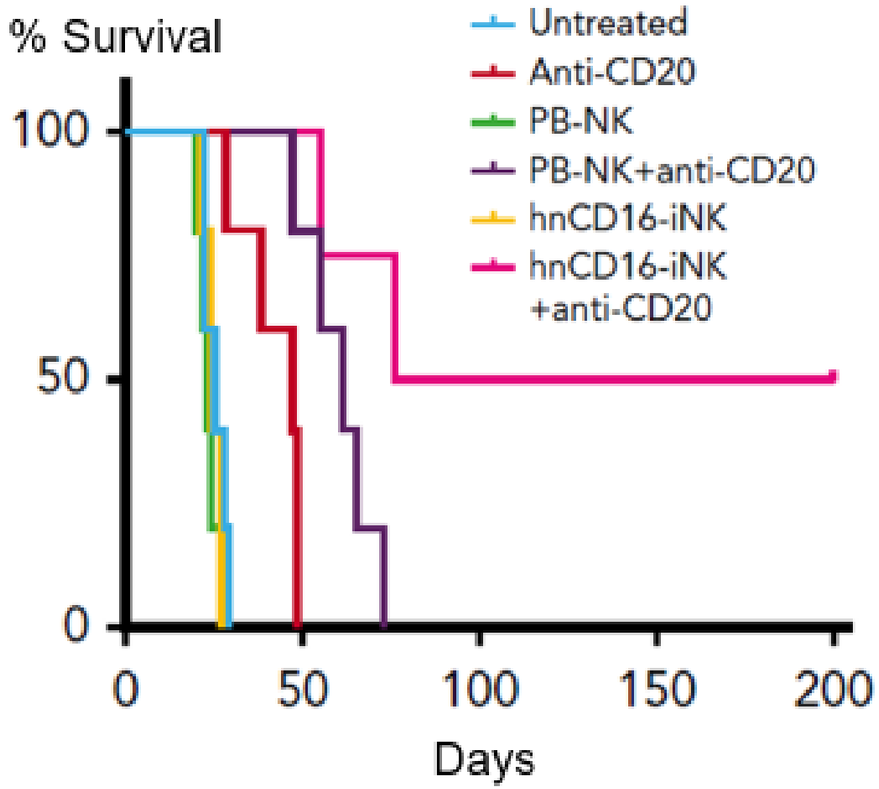
High-Affinity Non-Cleavable CD16 (FcγrIIIa)

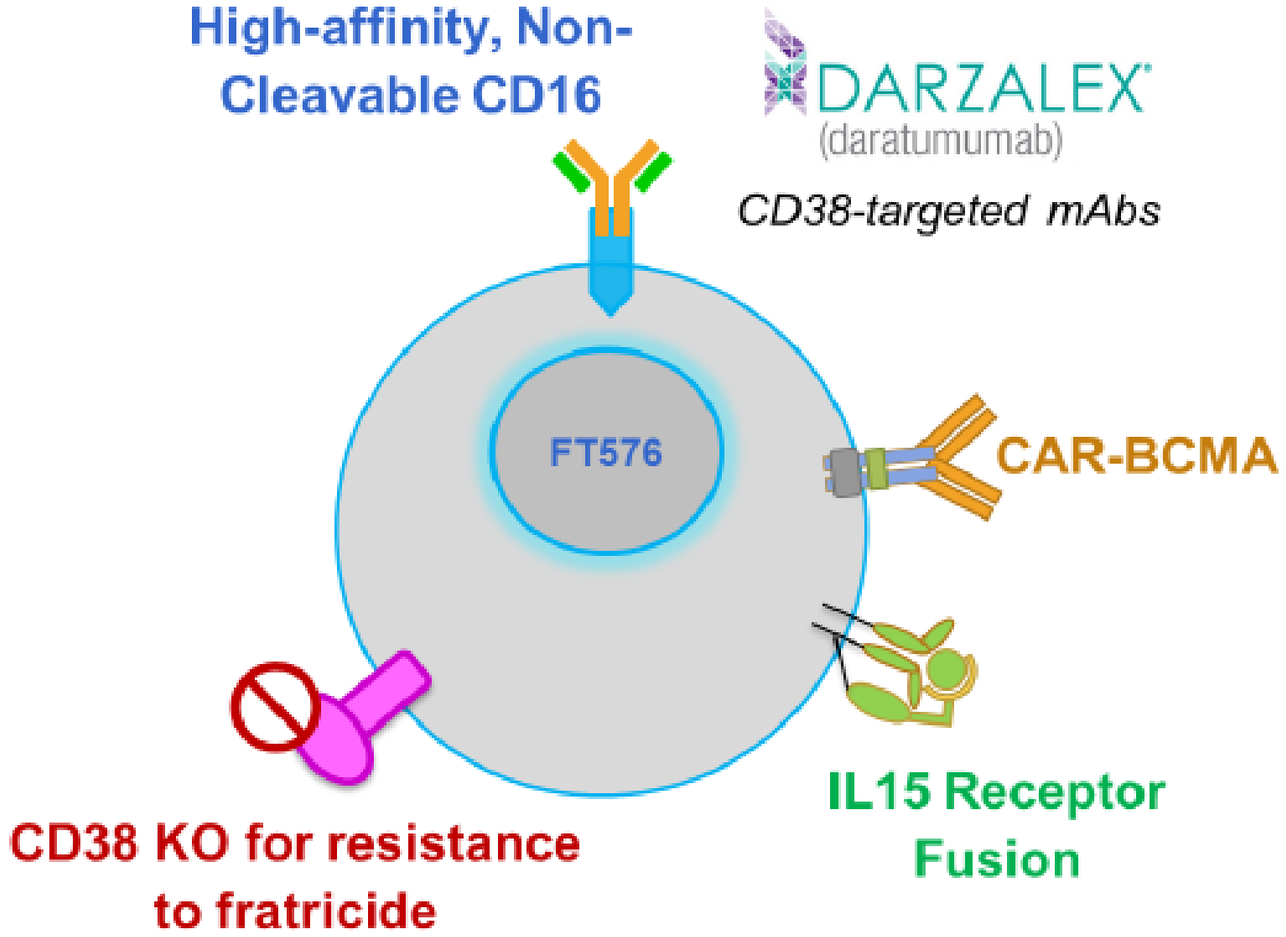


Raji Cancer Cells in Disseminated Xenograft Model of Lymphoma



Zhu et. al., Blood 2020

The Fourth Edit – Adding in CAR (FT576)



Note: This is a FATE Product Developed Independently of Janssen

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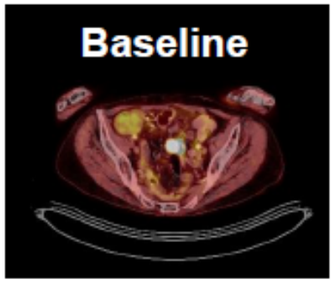
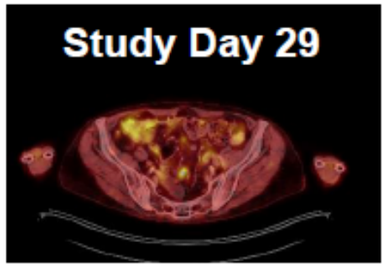
Early Clinical Data

- Partial response at Study Day 29 following first FT596 single-dose cycle
- Deepening of response at Study Day 75 following second FT596 single-dose cycle
- DoR = 3.7 months, comparable to that of auto CD19 CAR-T cell therapy among patients who achieve PR as BOR
- FT596 demonstrated consistent, detectable PK in peripheral blood following each single-dose treatment cycle



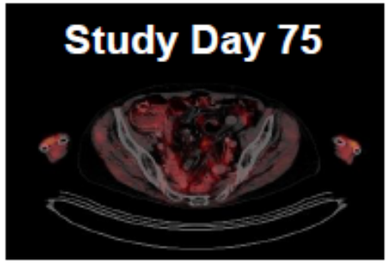
SPD
1292 mm^2

SUV
28



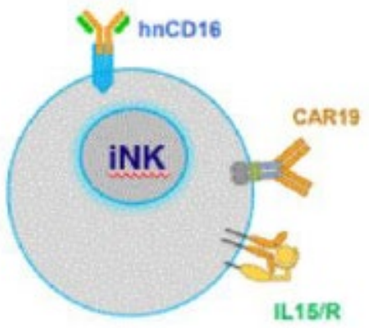
SPD
624 mm^2

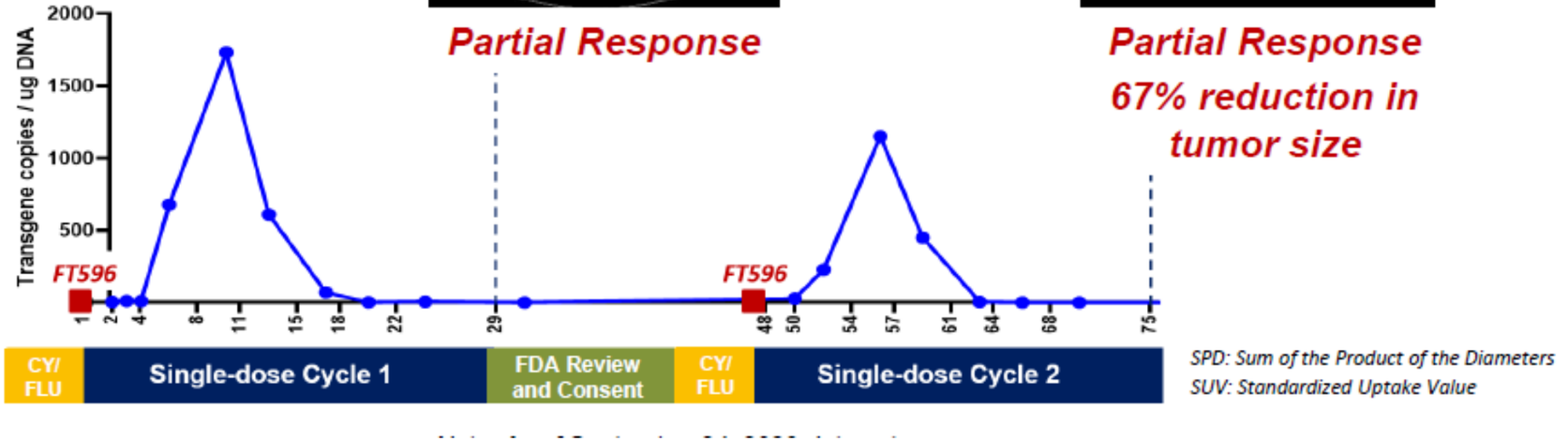
SUV
6.6



SPD
420 mm^2

SUV
2.6





SPD: Sum of the Product of the Diameters
SUV: Standardized Uptake Value

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Summary

1. Striking efficacy of Autologous CAR-T in Multiple Myeloma
   - Aspirational goal
   - Solid tumors (like PC) = work in progress

2. CD3 Redirectors: Active Agents / Room for Improvement

3. Allogeneic CAR iNK Cell Therapy
   - Early Days