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

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Additional information can be viewed by accessing this link: https://www.oncologysciencehub.com/OncologyAM2021/cilta-cel/Usmani/. Copies of this presentation obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASCO® and the author of this presentation.
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

  - 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.

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

Screening (28 days)
Apheresis
Bridging therapy <sup>a</sup> (as needed)
Cy (300 mg/m²) + Flu (30 mg/m²)
Cilta-cel infusion
Target: 0.75x10^6 (0.5–1.0x10^6)
CAR+ viable T cells/kg
Post-infusion assessments
Safety, efficacy, PK, PD, biomarker
Follow-up

Day -5 to -3
Day 1

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. <sup>a</sup>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).

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CARTITUDE-1: Progression-Free Survival

**Progression-Free Survival, Patients (%)**

- **All Patients**
  - Median: 22.8 months (95% CI, 22.8–NE)
  - 18-month PFS: All Patients: 66.0% (95% CI, 54.9–75.0)
  - Responders With sCR: 75.9% (95% CI, 63.6–84.5)

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

**Number at Risk**

- All Patients: 97
- Responders With sCR: 78

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

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T-Cell Redirectors

CD8 T cell

Signal 1 Activation

CD3

TAA1

Tumor Cell
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\textsuperscript{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. \textsuperscript{1}Smith Sci Transl Med 11(485):eaau7746. \textsuperscript{2}Verkleij HemaSphere 3(S1):230, Poster #PF556. \textsuperscript{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

Signal 1

CD8 T cell

CD3

TAA1

CD28

TAA2

Signal 2
FULL Activation

Tumor Cell
Next-Generation Cell Therapy

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

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

https://ir.fatetherapeutics.com/events-and-presentations
A Single Human Induced Pluripotent Stem Cell (iPSC)

A **renewable source for making cell products**

- Unlimited Clonal Expansion
- Multiplexed Engineering
- Extensive Characterization
- Potential to Differentiate into 200+ Cell Types
- Master Cell Lines and Banks
- Uniform in Composition

https://ir.fatetherapeutics.com/events-and-presentations
From iPSC to Natural Killer Cells (ipsc derived NK’s)

iPSCs  →  iCD34s  →  iNKs

Day 0  Day 10  Day 44

SSEA44

TRA181

CD34

CD43

CD45

CD56

10^6 iPSCs

> 1 million-fold expansion

> 10^{12} iNKs

https://ir.fatetherapeutics.com/events-and-presentations
Some Gene Editing (Engineering) In The Process

Cell Population Engineering

1 edit  2 edits  3 edits  4 edits

Correctly-edited  Incorrectly-edited

Single cell ipsc isolation, characterization and selection

Clonal Master Cell Line

https://ir.fatetherapeutics.com/events-and-presentations
**Three Edits**

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

*First-ever CRISPR-edited iPSC-derived Cell Therapy*

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**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.

- **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

% Survival

- Untreated
- Anti-CD20
- PB-NK
- PB-NK+anti-CD20
- hnCD16-iNK
- hnCD16-inK +anti-CD20

Days

0 50 100 150 200

Zhu et. al., Blood 2020
The Fourth Edit – Adding in CAR (FT576)

High-affinity, Non-Cleavable CD16

DARZALEX
(daratumumab)

CD38-targeted mAbs

FT576

CAR-BCMA

IL15 Receptor Fusion

CD38 KO for resistance to fraticide

Note: This is a FATE Product Developed Independently of Janssen
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
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