PF690

Preclinical Analysis of Ciltacabtagene Autoleucel Combination Strategies with T Cell Bispecifics and Daratumumab to Support Optimization of Clinical Benefit in Myeloma Patients

Douglas Marvel[1], Raj Kurupati[1], Gourav Choudhary[1], Joseph Portale[1], Mahipal Suraneni[1], Deeksha Vishwamitra[1], Nicholas Hein[2], Xuechen Wang[2], Nikoletta Lendvai[3], Jordan M. Schecter[3], J Blake Bartlett[4], Jason Brayer[4], and Vicki Plaks[1]

[1]Oncology Translational Research, Johnson and Johnson, Spring House, PA, USA; [2]Discovery Statistics Johnson and Johnson, Spring House, PA, USA; [3]Oncology Clinical Development Johnson and Johnson, Bridgewater, NJ, USA; [4]Oncology Global Medical Affairs Johnson and Johnson, Raritan, NJ, USA

Key Takeaway

Optimization of sequencing and combinations of research grade Cilta-cel CAR-T with other myeloma approved therapies can enhance its cytotoxicity

Conclusions

Response to CAR-T may be optimized by performing apheresis prior to treatment with T cell engagers or any treatment that may adversely affect T cell fitness

However, if T cell engagers are used during bridging, in combination or after CAR-T infusion, T cell fitness of the CAR-T drug product would be preserved

Furthermore, treatment regimens that take advantage of synergy with CAR-T (e.g. Daratumumab and/or T cell engagers used in direct sequence with CAR-T) could potentially enhance clinical responses in patients with compromised T cell fitness

Please scan QR code

Poster

Narrated poster video

Supplementary material

https://www.congresshub.com/EHA2025/Oncology#product-general-multiple-myeloma

Experimental Note:

CAR-T used for the experiments highlighted in this poster were a research grade variation of Ciltacabtagene autoleucel (Cilta-cel) manufactured using T cells obtained from healthy donors. Untransduced T cells are T cells activated in an identical manner, but lacking CAR transduction

Disclosures

All authors own equity in and/or are employed by Johnson and Johnson Innovative Medicine

Introduction

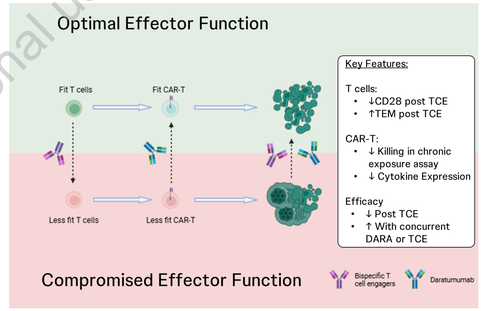
Ciltacabtagene autoleucel (Cilta-cel) is a multiple myeloma (MM) specific CAR-T cell therapy targeting BCMA. Teclistamab (Tec), and talquetamab (Tal) are MM directed T cell bispecifics (BsAbs) targeting BCMA and GPRC5D, respectively. All three therapies are designed to harness the anti-tumor activity of T cells. Yet, there is more to unravel about their use in concert and/or their preferred sequencing to ensure maximal therapeutic benefit. Likewise, the mechanism by which daratumumab (Dara), a monoclonal antibody targeting CD38, impacts the efficacy of Cilta-cel has not been fully realized. Our work aims to characterize the underlying mechanistic interactions between these therapies to potentially inform on their optimal clinical utilization as we push towards regimens with curative intent in MM.

Rationale

Key Clinical Findings Published To Date:

- CARTITUDE-2, Cohort C: Patients with prior exposure to BCMA targeted T cell engager (TCE) exhibited 57% vs. 97% ORR observed in CARTITUDE-1 with a similar patient population that had no exposure to BCMA targeted therapy[1]
- Retrospective multi-site review, RRMM (Ide-cel): Patients had 2.7 months median PFS with Ide-cel after TCE vs. 8.9 months in patients with no history of TCE[2]
- Mayo Clinic retrospective review 2018-23, RRMM (Cilta-cel and Ide-cel): TCE- experienced MM patients had 50% ORR when treated with BCMA CAR-T vs. 86% in patients who were TCE naïve[3]
- MSKCC site study, RRMM (Teclistamab): BCMA targeted therapy with Teclistamab led to antigen loss in only ~10% of patients[4]
- Key Takeaway: Better understanding of interactions between therapies and optimal sequencing is essential to enhance durable responses in MM

Graphical Summary



Results

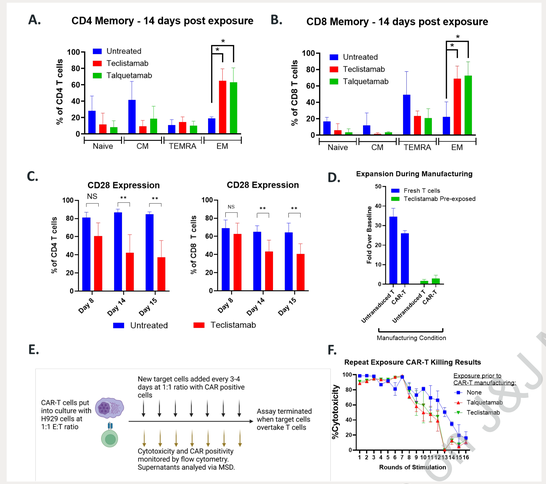


Figure 1. Prior exposure to bispecific T cell engagers polarize T cells towards a predominantly effector memory phenotype, characterized by low CD28 and compromised expansion capacity and effector function. **A.** Memory phenotyping performed on CD4 and **B.** CD8 T cells after a 14-day pretreatment with Teclistamab or Talquetamab. Indicated groups were identified by CCR7 and CD45RA expression. Naïve (CCR7+CD45RA+), CM (CCR7+, CD45RA-), TEMRA (CCR7-CD45RA+), and EM (CCR7-. CD45RA-). **C.** CD28 expression on these same CD4 and CD8 T cells. **D.** Expansion during research grade CAR-T manufacturing using TEC exposed T cells treated as in parts **A-C**. **E.** Experimental schema for repeat exposure assay using CAR-T. F. Results from repeat exposure assay using CAR-T made from in vitro TEC and TAL pre-exposed T cells as in parts **A-C.**

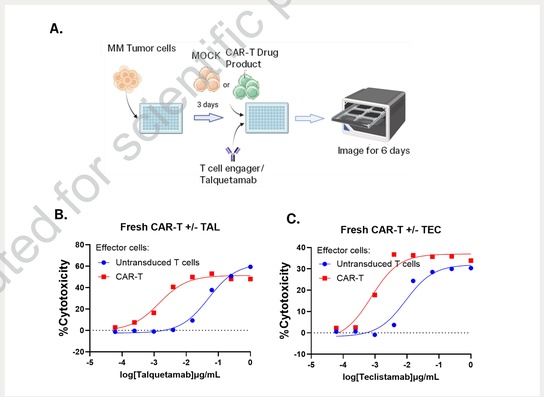


Figure 2. Simultaneous exposure to research grade CAR-T and bispecific T cell engagers increases the cytotoxic potential of both drugs. **A.** In vitro experimental schema. **B.** Cytotoxicity from incucyte assay expressed as transformed AUC of spheroid growth curves. X axis represents concentration of Talquetamab (TAL). Untransduced T cells and CAR-T drug product identify the responding T cell populations. Data shown for Talquetamab and **C.** Teclistamab. (D-H in next column).

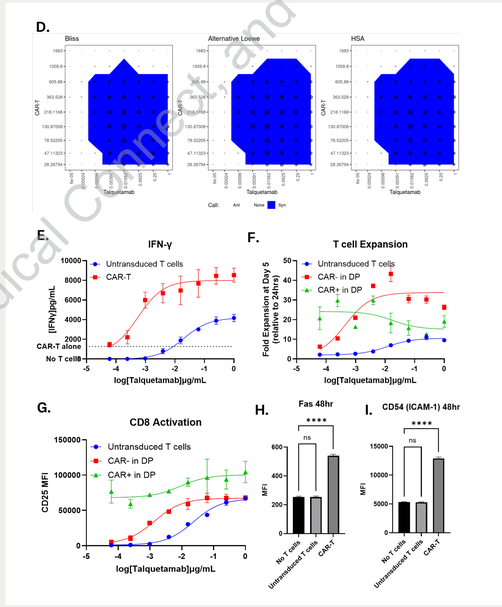


Figure 2 (Cont'). Simultaneous exposure to research grade CAR-T and bispecific T cell engagers increases the cytotoxic potential of both drugs. **D.** Synergy analysis using this assay and varying CAR positivity and Talquetmab concentration. **E.** IFNγ, **F.** T cell expansion, and **G.** CD8 T cell activation from in vitro spheroid assay with Talquetamab shown in Untransduced T cells and drug product (DP) **H.** Expression of Fas and **I.** CD54 on H929 cells from spheroid assay either alone, or with the indicated T cell population added. (A-C in previous column).

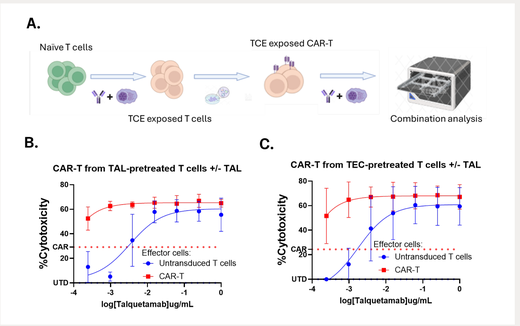


Figure 3. Simultaneous exposure to bispecific T cell engagers pre-exposed research grade CAR-T together with bispecific T cell engagers increases the cytotoxic potential of both drugs. **A.** *In vitro* experimental schema. Pre-exposure in this experiment was done with Talquetamab. **B.** Cytotoxicity from incucyte assay expressed as the transformed AUC of spheroid growth curves. X axis represents concentration of TAL. Untransduced T cells and CAR-T identify the responding T cell populations. Dotted lines represent cytotoxicity level with no Talquetmab. Data shown for Talquetamab and **C.** Teclistamab.

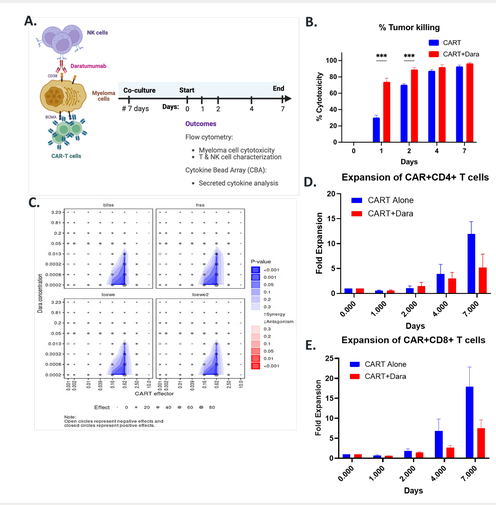


Figure 4. Addition of Dara to research grade CAR-T induces potent myeloma cell killing. **A.** Experiment schema. **B.** Cytotoxicity results over 7-day assay. **C.** Synergy analysis of interactions between Dara and Cilta-cel. **D.** CD4 and **E.** CD8 expansion throughout the assay.

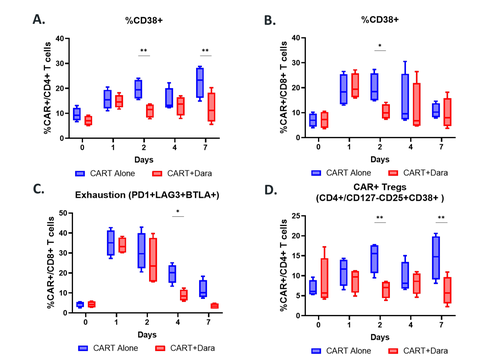


Figure 5. Enhanced research grade CAR-T cell fitness with daratumumab combination. **A.** CD38 expression on CD4 and **B.** CD8 T cells throughout the duration of the assay shown in Figure 4. **C.** Impact of Dara on proportion of exhausted CAR+CD8+ cells when Boolean gated on PD1, LAG3 and BTLA. **D.** Impact of Dara on proportion of CAR+ Treg populations defined by gating on CD4+/CD127-CD24+/CD38+ cells.

References

1. Blood. 2023 Jan 19;141(3):219-230. doi: 10.1182/blood.2022015526
2. J Clin Oncol. 2023 Apr 10; 41(11): 2087–2097
3. Blood Cancer Journal volume 14, Article number: 122 (2024)
4. Blood. 2024 May 10:blood.2023023557. doi: 10.1182/blood.2023023557

Multiple Myeloma

Presented by V. Plaks at EHA; [June 13th, 2025]; [Milan, Italy]