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Earlier Ciltacabtagene Autoleucel Use and Better Immune Fitness Based on Correlative Analysis of Peripheral Blood and Bone Marrow Tumor Microenvironment From CARTITUDE-4

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Key Takeaway

Our data support treating patients with RRMM with cilta-cel in earlier LOT as this may facilitate improved immunocompetency, supporting durable CAR-T responses and improved patient outcomes

Conclusions

- Cilta-cel treatment in patients with earlier LOT is associated with improved clinical outcomes such as PFS and OS
- Post cilta-cel infusion, there is an enrichment of gene expression signatures associated with anti-tumor myeloid cells and an inflammatory state, as well as T-cell activation and antigen presentation
- Long-term durable responses are associated with increased TCR diversity and preferential expansion of CD4 memory T cells
- Earlier use of cilta-cel can support longer PFS given the more immunocompetent TME and the better peripheral immune fitness at baseline in earlier LOT

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Poster

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Disclosures

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Background

- Ciltacabtagene autoleucel (cilta-cel) has previously demonstrated profound efficacy in both the CARTITUDE-1 and CARTITUDE-4 studies[1-6]
- CARTITUDE-1 was a phase 1/2 study in patients with relapsed/refractory multiple myeloma (RRMM) who had received 3 prior lines of therapy (pLOT) or who were double-refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD) and had been exposed to a PI, IMiD, and anti-CD38 monoclonal antibody[1]
  - One-third of patients were treatment and progression free for ≥5 years after a single cilta-cel infusion[2]
- CARTITUDE-4 was a phase 3 study in patients who had been diagnosed with multiple myeloma and had received 1–3 pLOT, including a PI and IMiD, and who were lenalidomide refractory[3]
  - A significant overall survival (OS) benefit was observed, with a higher proportion of cilta-cel patients achieving deep, sustained minimal residual disease negativity vs standard of care[4-6]
- In both studies, progression-free survival (PFS) was shown to improve when cilta-cel was used earlier in RRMM:
  - Median PFS was 34.9 months for those who had received ≥3 pLOT, 50.4 months for 3 pLOT, and not reached (NR; median follow-up, 34 months) for 1 pLOT
- In both studies, earlier treatment with cilta-cel was also associated with OS extension

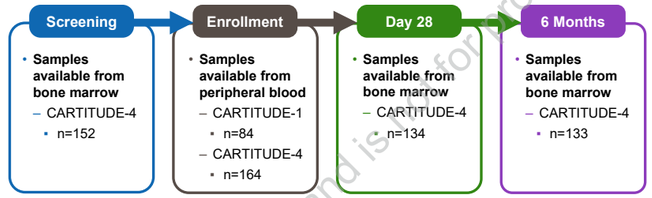
Aims

- To determine if cilta-cel treatment in earlier LOT leads to improved outcomes due to a more immunocompetent tumor microenvironment (TME), we evaluated TME biomarkers at various pLOT to assess long-term clinical response impact

Methods

- 176 patients in CARTITUDE-4 and 97 patients in CARTITUDE-1 received cilta-cel as study treatment (**Figure 1**)

Figure 1: A breakdown of the samples acquired for correlative analysis in CARTITUDE-1 and -4



TME was evaluated in bone marrow aspirates (BMA) from CARTITUDE-4 by bulk RNA sequencing

- Gene set variation analysis[7] and mixed-effects models were used to identify gene signatures and pathways modulated longitudinally and in association with PFS as well as pLOT
- T-cell receptor (TCR) repertoire analysis was also performed in BMA from a subset of patients in CARTITUDE-1[8]

Immunophenotyping by flow cytometry was performed on peripheral blood samples collected from both the CARTITUDE-1 and CARTITUDE-4 studies

- Immune fitness at baseline was assessed in patients by pLOT and in association with PFS using nonparametric statistics

Results

CARTITUDE-4: TME bulk RNA sequencing

Gene expression analyses suggest:

- Depleted B cells at day (D) 28 followed by partial recovery at 6 months (6M), accompanied by enhanced immunoglobulin V(D)J recombination (data not shown)
- Increased neutrophil degranulation and extravasation at D28 and 6M (**Figure 2A,** degranulation)
- Increased tumor-associated macrophages (TAMs) at D28 and 6M (**Figure 2B–D**)
  - Concurrent upregulation of cytokine signaling pathways mediated by M1 macrophages (eg, interleukin [IL]-12, but not by M2 macrophages [eg, transforming growth factor [TGF]-β]), suggest TAMs are likely M1 (anti-tumor) macrophages
- Increased activation, differentiation, and proliferation of diverse T-cell subtypes at D28 and 6M (**Figure 3A** and **B,** T-cell receptor alpha chain [TCRA] and cytotoxic T lymphocyte [CTL] pathways)
- Elevated major histocompatibility complex (MHC) I and II pathways suggesting robust antigen presentation capacity at D28 and 6M (**Figure 3C,** MHC pathway)

Figure 2: Enrichment of (A) neutrophil degranulation, (B) tumor-associated macrophages, (C) IL-12 STAT4 pathway, (D) TGF-β signaling at baseline, D28, and 6M

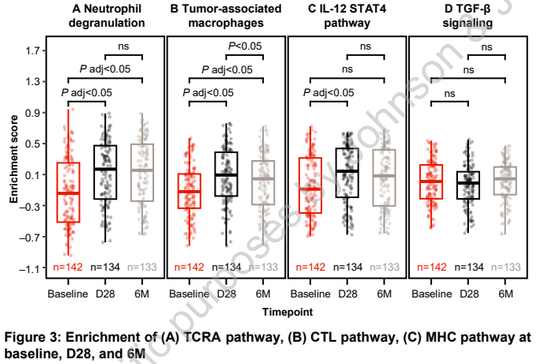
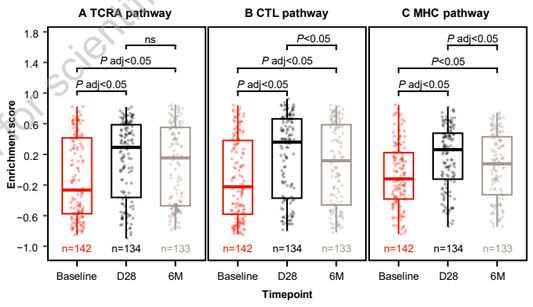


Figure 3: Enrichment of (A) TCRA pathway, (B) CTL pathway, (C) MHC pathway at baseline, D28, and 6M

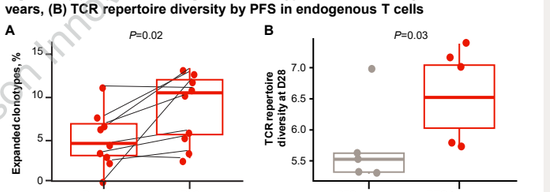


P adj: adjusted *P* value; STAT, signal transducer and activator of transcription.

CARTITUDE-1: T-cell sequencing

- T-cell receptor (TCR) sequencing was performed at D28 post infusion in a subset of patients in CARTITUDE-1
- Patients who achieved long-term durable responses (PFS ≥5 years) had:
  - Higher proportion of expanded clonotypes within CD4 memory T cells from baseline to D28 post infusion (**Figure 4A**)[8]
  - Higher TCR repertoire diversity in endogenous T cells (**Figure 4B**),[8] which further highlights the importance of a robust TCR activation in driving long-term durable response as observed in patients with fewer pLOT in CARTITUDE-4

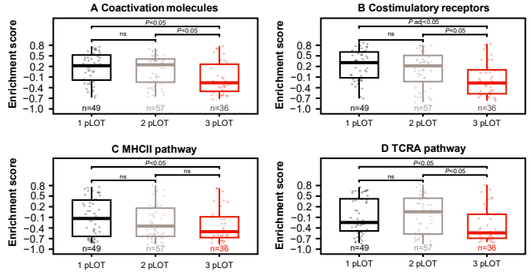
Figure 4: (A) Expanded endogenous clonotypes in CD4 memory T cells in PFS ≥5 vears, (B) TCR repertoire diversity by PFS in endogenous T cells



CARTITUDE-4: TME immunocompetence by pLOT

- Patients with 1 or 2 vs 3 pLOT had a more immunocompetent TME at baseline, as suggested by higher levels of costimulatory molecules, CD4+ T cell antigen-presenting machinery (MHCII), and TCRA pathway (**Figure 5**)
  - Higher levels of these gene signatures in TME at baseline trended with longer PFS (data not shown)

Figure 5: Baseline enrichment of (A) coactivation molecules, (B) costimulatory receptors, (C) MHCII pathway, (D) TCRA pathway by pLOT



CARTITUDE-4: TME immunosuppressive activity by PFS and pLOT

Gene expression analyses suggest:

- At 6M vs baseline, patients with shorter PFS (≤18 months [18M]) had:
  - Increased regulatory T cells (T_{regs}; **Figure 6A**), suggestive of an increasingly immune-suppressive TME
  - Upregulated epithelial-to-mesenchymal transition (EMT) and phosphoinositide 3-kinase (PI3K)/AKT pathway signatures over time (**Figure 6B** and **C**), suggestive of a more hostile TME[9,10]
- From baseline to D28 or 6M, upregulation of these gene signatures in the TME over time was also associated with more pLOT (**Figure 7A–C**)

Figure 6: Enrichment of (A) T_{reg}, (B) EMT signature, (C) PI3K/AKT pathway by PFS

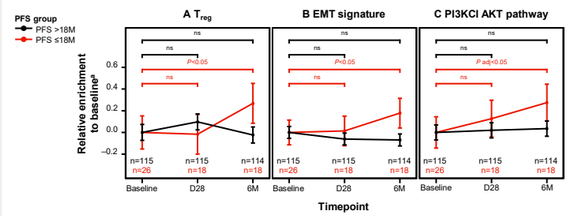
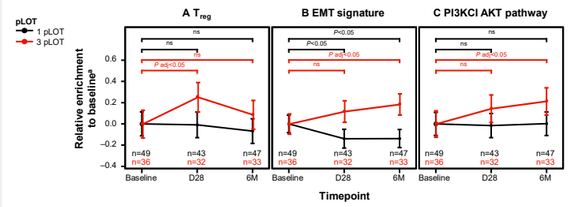


Figure 7: Enrichment of (A) T_{reg}, (B) EMT signature, (C) PI3K/AKT pathway by pLOT

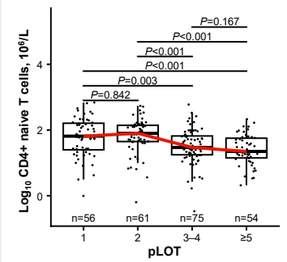


[a]Error bars represent estimated 95% confidence intervals.

CARTITUDE-1 and -4: T-cell fitness

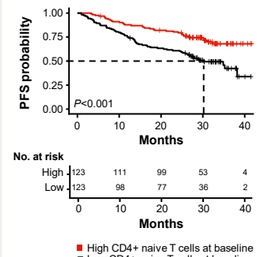
- Peripheral immune fitness at baseline was significantly enhanced in patients with fewer pLOT but not in patients with ≥3 pLOT (**Figure 8**)
  - CD4+ naive T cells were previously shown to associate with long-term efficacy with other anti–B-cell maturation antigen chimeric antigen receptor T cells (CAR-T)[11,12]
- Association of PFS with T-cell fitness in drug product was previously reported in CARTITUDE-1 (**Figure 9**)[2,13]

Figure 8: CD4+ naive T cells at baseline grouped by pLOT[a]



[a]Ad hoc analyses integrating data from CARTITUDE-1 and CARTITUDE-4 studies.

Figure 9: PFS stratified by CD4+ naive T cells at baseline[a]



[a]Ad hoc analyses integrating data from CARTITUDE-1 and CARTITUDE-4 studies.

References

1. Berdeja JG, et al. *Lancet* 2021;398:314-24. 2. Jagannath S, et al. *J Clin Oncol* 2025;43:2766-71. 3. Martin T, et al. *J Clin Oncol* 2023;41:1265-74. 4. San-Miguel J, et al. *N Engl J Med* 2023;389:339-47. 5. Mateos M-V, et al. *Clin Lymphoma Myeloma Leuk* 2024;24(suppl 2):S290. 6. Popat R, et al. *Transplant Cell Ther* 2025; 31(suppl):S35. 7. Hanzelmann S, et al. *BMC Bioinformatics* 2013;14:7. 8. Vieira dos Santos J, et al. *Blood Adv* 2026;10:604-7. 9. Alameda D, et al. *Haematologica* 2020;105:e470-3. 10. Heinemann L, et al. *Front Oncol* 2022;12:874325. 11. Ledergor G, et al. *Blood Adv* 2024;8:3562-75. 12. Rasche L, et al. *Blood* 2024;143:305-10. 13. Montes de Oca R, et al. Presented at ASH; December 9–12, 2023; San Diego, CA, USA.

Multiple Myeloma

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