Ciltacabtagene Autoleucel Out-of-Specification Manufacturing Outcomes Improve With Earlier Lines of Therapy

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Key Takeaway

Rates of first and overall manufacturing success were higher when using cells collected from patients with 1-3 versus ≥4 prior lines of therapy

Conclusions

Overall, 99% of products manufactured using cells from patients with 1-3 pLOT (6.5% received an OOS product) compared with 97% for ≥4 pLOT (9.2% received an OOS product)

T-cell attributes associated with manufacturing outcomes were also improved in starting material collected from patients with 1-3 versus ≥4 pLOT

Remanufacture of product using original or recollected apheresis material often results in additional OOS outcomes, which may further delay patient treatment

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Poster

Narrated poster video

Acknowledgments

This study was funded by Janssen Research & Development, LLC, and Legend Biotech USA Inc.

Introduction

- Ciltacabtagene autoleucel (cilta-cel) is a B-cell maturation antigen (BCMA)–directed chimeric antigen receptor (CAR) T-cell therapy approved for adults with lenalidomide-refractory multiple myeloma as early as after 1 prior line of therapy (pLOT)
  - Cilta-cel is manufactured using autologous T cells, which presents inherent variability in the initial starting material and subsequent manufactured product, including out-of-specification (OOS) drug products that do not meet health authority specifications
- Quality attributes of patient-derived T cells are the predominant contributors to OOS manufacturing outcomes[1]
  - Manufacturing in-specification drug products is associated with the enrichment of naive and central memory T-cell subpopulations, which are more abundant in material collected from patients with relatively fewer pLOT[2]
  - T-cell characteristics associated with improved manufacturing outcomes (ie, in-specification drug product) are associated with prior treatment history[1]

Objective

- Examine cilta-cel manufacturing outcomes across multiple pLOT

Methods

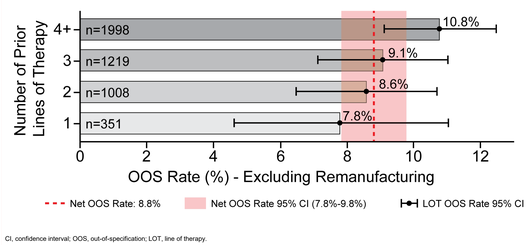
- Commercial cilta-cel manufacturing data (July 2024-October 2025) were analyzed to
  - Identify determinants of manufacturing outcomes
  - Define biomarkers predictive of manufacturing success and
  - Assess manufacturing results following OOS-driven remanufacturing or recollection
- Manufacturing success refers to the successful production of CAR T-cell products that meet specifications[1,2]

Results

Manufacturing outcomes: OOS rates

- OOS rates were reduced when using T cells from patients with fewer pLOT (7.8% with 1 pLOT to 10.8% with ≥4 pLOT; N=4576; Figure 1)

Figure 1. OOS rates

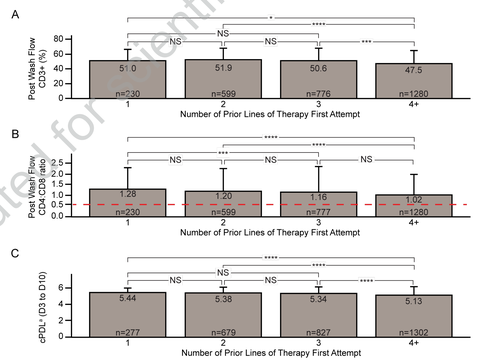


CI, confidence interval; OOS, out-of-specification; LOT, line of therapy.

Biomarkers predictive of manufacturing success

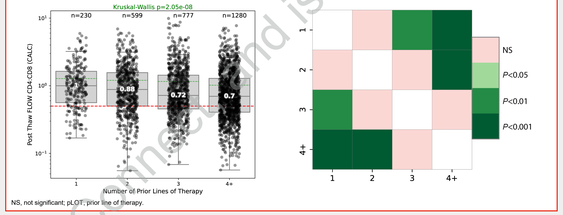
- CD3+ cell recovery at the initiation of manufacturing was favorable in patients with fewer pLOT versus ≥4 pLOT (Figure 2A)
- The initial post-thaw cellular CD4:CD8 ratio improved by 30% with fewer pLOT (average CD4:CD8 ratio, 1.0 with 1 pLOT vs 0.7 with ≥4 pLOT; Figure 2B, Figure 3)
  - CD4:CD8 ratio >0.5 may contribute to better in-specification, first-time manufacturing outcomes
  - In prior studies, presence of healthy CD4+ CAR-T cells is associated with improved clinical outcomes[3,4]
- Recovery of viable cells before lentiviral vector transduction and cumulative population doubling level (cPDL) of cells improved (up to 6%) with fewer pLOT (P<0.05 for both; Figure 2C)

Figure 2. (A) CD3+ cell recovery rates, (B) Cellular CD4:CD8 ratios and (C) Cumulative population doubling level of cells in the first manufacturing attempt



cPDL, cumulative population doubling level; D, Day; NS, not significant; OOS, out-of-specification; *Higher cPDL is desirable. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

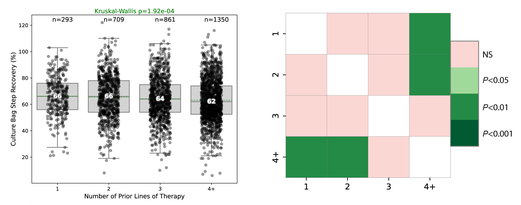
Figure 3. Post-thaw CD4:CD8 ratios in the first manufacturing attempt across pLOT



NS, not significant; pLOT, prior line of therapy.

- Activation bag recovery was significantly improved with 1 or 2 pLOT vs ≥4 pLOT (Figure 4)

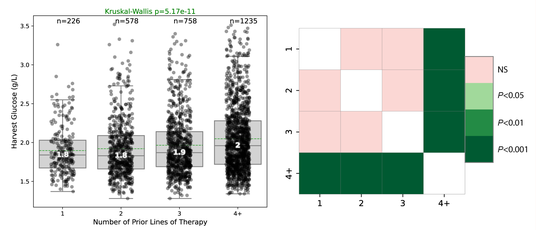
Figure 4. Activation bag recovery in the first manufacturing attempt



NS, not significant.

- Markers of metabolic activity, including glucose consumption and lactate production, were significantly improved with fewer pLOT (average improvement of 10% for material from patients with 1 pLOT versus more pLOT; Figure 5)

Figure 5. Glucose consumption by CAR-T cells

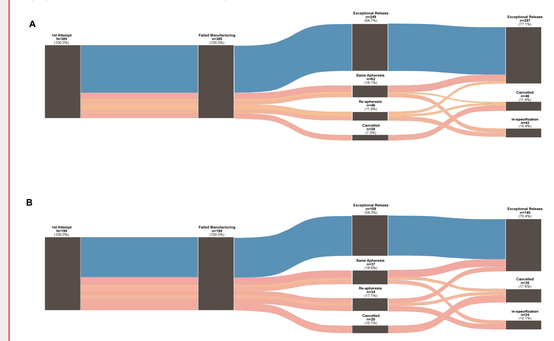


CAR, chimeric antigen receptor; NS, not significant.

Manufacturing outcomes

- Among cilta-cel OOS outcomes from all pLOT (n=385):
  - 64.7% were released through an expanded access program without remanufacturing (Figure 6A)
  - 28% (n=108) of the initial OOS outcomes underwent remanufacturing:
    - 11.9% (n=46) that resulted in cancellation
    - 10.9% (n=42) that resulted in within-specification outcomes after the remanufacturing attempt
  - 7.3% of the initial OOS outcomes were canceled

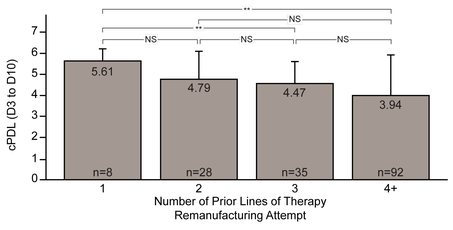
Figure 6. Cilta-cel OOS outcomes across (A) all lines of therapy and (B) ≥4 prior lines of therapy



cilta-cel, ciltacabtagene autoleucel; OOS, out-of-specification.

- Remanufacturing attempts using material from patients with ≥4 pLOT (n=199) resulted in the same or additional OOS results or cancellations as the first manufacturing OOS outcome (67% of attempts [n=36]; Figure 6B)
  - 35.7% (n=71) of the initial OOS outcomes underwent remanufacturing, including:
    - 17.6% (n=35) resulted in cancellation
    - 12.1% (n=24) resulted in within-specification outcomes after remanufacturing
- cPDL of cells undergoing remanufacturing improved with fewer pLOT (Figure 7)

Figure 7. Cumulative population doubling level of cells in the remanufacturing attempt



cPDL, cumulative population doubling level; D, Day; NS, not significant; **P<0.01.

Recollection outcomes

- Remanufacturing from recollection of new apheresis material was requested in 12% of initial OOS cases as a result of insufficient remaining material or because of concerns about the effects of prior therapies, suggesting long-lasting impact of prior treatments and/or disease characteristics
  - Remanufacturing attempts using new apheresis material (n=46) resulted in similar or worse outcomes in 31% of cases, and 20% of cases resulted in cancellation of the order
  - Furthermore, cancellation rate for remanufacturing with ≥4 pLOT was 17.6% (n=35)

References

1. Baguet et al. *Blood Adv.* 2024;8:337-342. **2.** Ayala et al. *J Exp Med.* 2024;221:e20230903. **3.** Ledergor et al. *Blood Advances.* 2024;8(13):3562-3575. **4.** Parekh et al. Poster presented at American Society of Hematology; December 6-9, 2025; Orlando, FL, USA.

Multiple Myeloma