Poster
P1425

Real-World Manufacturing Experience of Axicabtagene Ciloleucel for Patients Treated in Second Line Versus Third Line of Therapy and Beyond

Jason R. Westin, MD, MS, FACP[1]; Dalia Rangel, BSc[2]; José G. Ramírez, MSc, PhD[2]; David Myers, BS[2]; Laura Alquist, BSBM[2]; Clare Spooner, MBBS, BSc[2]; Harry W. Smith, MSc, BSc[2a]; Rhine R. Shen, PhD[2]; Simone Filosto, PhD[2]; and Frederick L. Locke, MD[3]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Kite, a Gilead Company, Santa Monica, CA, USA; and [3]Moffitt Cancer Center, Tampa, FL, USA

BACKGROUND

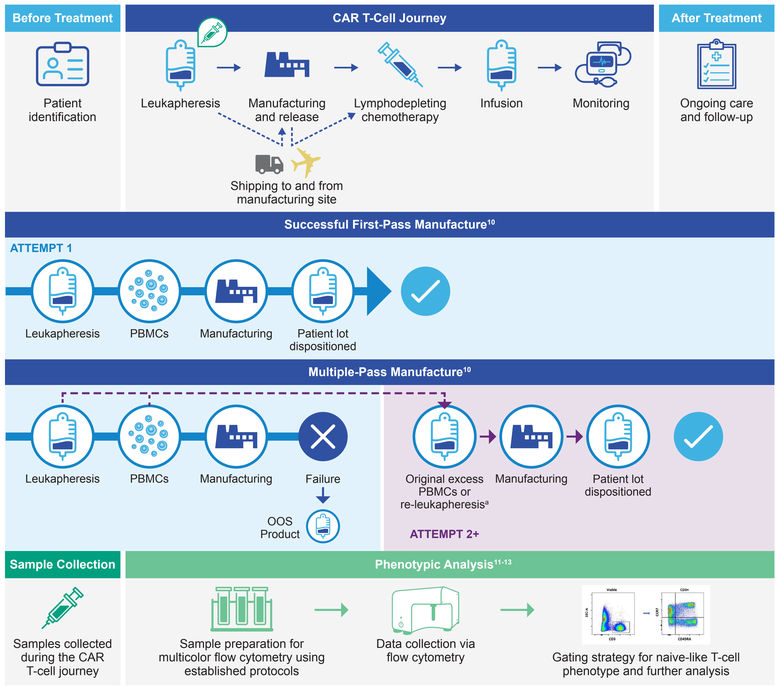
- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy that is approved in many countries for patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) or follicular lymphoma (FL)[1,2]
  - Axi-cel is approved for patients with LBCL refractory to or who relapsed within 12 months of first-line chemoimmunotherapy based on the Phase 3 ZUMA-7 study (NCT03391466) and in the third-line or later (3L+) setting based on the Phase 2 ZUMA-1 (NCT02348216; R/R LBCL) and ZUMA-5 (NCT03105336; R/R FL) studies[3-5]
- Axi-cel is manufactured for commercial use in the second-line (2L) and 3L+ settings at 3 sites globally and is administered at over 450 authorized/qualified treatment centers worldwide
- In the clinical trial setting, it was demonstrated that timely infusion of CAR T-cell therapy was associated with improved survival outcomes for patients with R/R LBCL[6]
  - In the real-world setting, rapid and efficient manufacturing remains important to maximize the number of patients who can successfully receive therapy in a timely manner
  - Efficient manufacturing of axi-cel and timely delivery may be further impacted in the real-world setting by challenges associated with higher patient numbers, a more heterogenous patient pool, and a larger number of manufacturing sites and treatment centers compared with the clinical trial setting
- Successful manufacturing of a patient lot within specification on the first-pass attempt can reduce wait times for CAR T-cell infusion[7] that can occur with manufacturing failures and multiple-pass manufacture
- It was previously demonstrated that axi-cel manufacturing outcomes for patients in the United States and Europe in the 3L+ real-world setting are robust and reliable[8-10]
  - Additionally, it was shown that real-world manufacturing outcomes in patients who received axi-cel in 2L in the United States closely approximated the successful outcomes observed in the ZUMA-7 clinical trial setting[10]
- In an analysis of patient leukapheresis material in the clinical trial setting for patients in 2L (ZUMA-7) versus 3L+ (ZUMA-1), a higher percentage of naive-like T cells was observed in the leukapheresis material for 2L patients versus 3L+, and this was numerically associated with improved response in 2L[11]
- To fully understand the manufacturing outcomes of axi-cel manufactured for patients in 2L versus 3L+, it is of interest to examine the real-world manufacturability of axi-cel in 2L versus 3L+ as well as the potential impact of line of therapy on the manufacturability of patient leukapheresis material

OBJECTIVE

- To compare the real-world axi-cel manufacturing experience and clinical trial leukapheresis material characteristics for patients in 2L versus 3L+

METHODS

Figure 1. Overview of Axi-Cel Treatment Journey



[a] In most cases, the subsequent manufacturing attempt is initiated with the remaining PBMCs from previous leukapheresis (only a few patients undergo re-leukapheresis for the following manufacturing attempt).
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; OOS, out of specification; PBMC, peripheral blood mononuclear cell.

- The axi-cel treatment journey includes leukapheresis, manufacturing, and infusion (**Figure 1**)

METHODS *(Continued)*

Data Sources

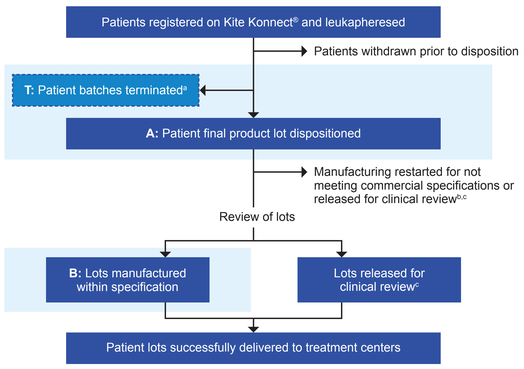
Real-World Manufacturing

- Patients registered on Kite Konnect® globally and leukapheresed for axi-cel treatment in 2L LBCL or any 3L+ indication between April 19, 2022 (the date of first leukapheresis for patients treated in 2L following commercial availability of axi-cel in this line of therapy), and January 3, 2024

Clinical Leukapheresis Phenotypes

- Evaluable patients with R/R LBCL in 3L+ enrolled in ZUMA-1 Cohorts 1 and 2[4]
- Evaluable patients with R/R LBCL in 2L enrolled in ZUMA-7[3]
- Leukapheresis material attributes were measured using multicolor flow cytometry, as previously described (**Figure 1**)[11-13]

Figure 2. First-Pass Manufacturing Success Rate Definition



First-Pass Manufacturing Success Rate Calculation: $B \div (A + T)$

Light blue boxes shade the key elements that factor into the first-pass manufacturing success rate calculation.
[a] Terminated but not withdrawn.
[b] Not all patient batches are restarted.
[c] Product that does not meet commercial specification but is acceptable for clinical specification.

Outcomes and Statistical Analysis

Manufacturing Outcomes and Statistical Analysis

- The primary manufacturing metric examined in this study was first-pass manufacturing success rate (FP-MSR), defined as the percentage of first-attempt patient lots dispositioned as manufactured within specification out of the total number of first-attempt patient lots dispositioned plus those terminated, excluding those terminated for withdrawn patients, in the period (**Figure 2**)
  - The difference in FP-MSR in 2L versus 3L+ was evaluated by fitting a generalized linear model with a binary distribution and performing a fixed effect test, and all calculations were done using SAS (TS1M7)

Translational Outcomes and Statistical Analysis

- ZUMA-7 (2L) and ZUMA-1 (3L+) patient leukapheresis material phenotypes were measured as the percentage of cells with naive-like T-cell phenotype (defined as CCR7+CD45RA+ within CD3+ cells)
  - Leukapheresis material phenotypes were analyzed using a Wilcoxon rank sum test

RESULTS

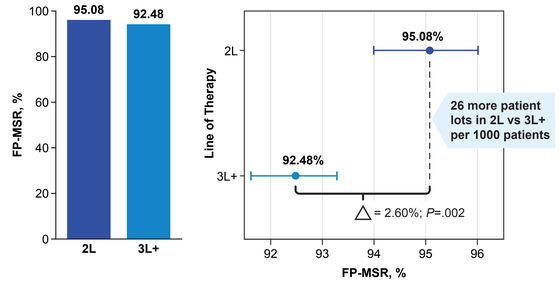
2L Versus 3L+ Manufacturing Experience

Table 1. Patients and FP-MSR for Axi-Cel in 2L Versus 3L+

Variables	2L	3L+
Date range	April 19, 2022-January 3, 2024	
Registered on Kite Konnect® and leukapheresed, N	1341	2834
FP-MSR, %	95.08	92.48
P value	.002	

2L, second line; 3L+, third line or later; axi-cel, axicabtagene ciloleucel; FP-MSR, first-pass manufacturing success rate.

Figure 3. Lots Successfully Manufactured in First Manufacturing Attempt Per 1000 Patients in 2L Versus 3L+



2L, second line; 3L+, third line or later; FP-MSR, first-pass manufacturing success rate.

- A total of 4175 patients were included in this analysis, including 1341 treated in 2L and 2834 treated in 3L+ (**Table 1**)
- Patients in 2L had a greater FP-MSR (95.08%) than patients in 3L+ (92.48%) which was statistically significant (*P*=.002)
  - This difference (2.60%) suggests that 26 more lots of axi-cel are successfully manufactured per 1000 in the first attempt for patients in 2L versus patients in 3L+ (**Figure 3**)

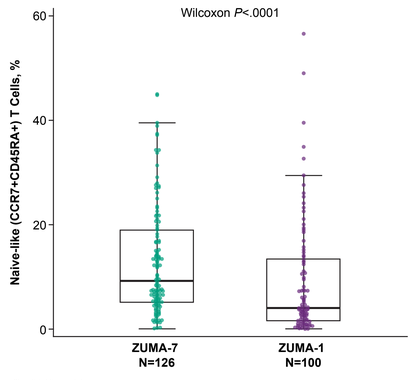
T-Cell Characteristics in Leukapheresis Material in 2L Versus 3L+

Table 2. T-Cell Characteristics in Patient Leukapheresis Material in 2L (ZUMA-7) Versus 3L+ (ZUMA-1)

Variables	2L	3L+
Patients with evaluable leukapheresis material, N	126	100
Median (range) proportion of naive-like T cells, %	9.28 (0.20-45.07)	4.11 (0.09-56.60)
P value	<.0001	

2L, second line; 3L+, third line or later.

Figure 4. Proportion of Naive-Like T Cells in Patient Leukapheresis Material in 2L (ZUMA-7) Versus 3L+ (ZUMA-1)



2L, second line; 3L+, third line or later.

- Patients in 2L had a significantly higher median percentage of naive-like cells in leukapheresis material (9.28% [range, 0.20-45.07]) versus patients in 3L+ (4.11% [range, 0.09-56.60]; *P*<.0001; **Table 2**)
- In the leukapheresis material, patients in 2L displayed a median of approximately 2 times as many naive-like T cells versus patients in 3L+ (**Figure 4**)

CONCLUSIONS

- In this analysis, a greater proportion of patients who received axi-cel in 2L had product successfully manufactured at first attempt versus those in 3L+, and this difference was statistically significant (*P*=.002)
  - The 2.60% difference in FP-MSR observed for patients in 2L versus 3L+ could result in a markedly greater number of patients in earlier lines of therapy successfully receiving axi-cel on the first manufacturing attempt
  - Given that higher FP-MSR lessens the need for multiple manufacturing attempts, patients in 2L could potentially experience shorter times from leukapheresis to product infusion (vein-to-vein time) versus patients in 3L+. However, further studies are needed to fully examine the relationship between line of therapy and vein-to-vein time
- In a phenotype analysis of patients' leukapheresis material in the 2L versus 3L+ R/R LBCL clinical trial setting, patients in 2L showed a higher frequency of naive-like T cells versus patients in 3L+
- These results suggest a benefit in axi-cel manufacturability when employing axi-cel in earlier lines of therapy, along with the potential for capturing a greater naive-like T-cell population in the initial leukapheresis material with earlier CAR T-cell intervention

REFERENCES

1. YESCARTA® (axicabtagene ciloleucel). Prescribing information. Kite Pharma, Inc; 2024.
2. YESCARTA® (axicabtagene ciloleucel) [summary of product characteristics]. Amsterdam, The Netherlands: Kite Pharma EU B.V.; 2024.
3. Locke FL, et al. *N Engl J Med*. 2022;386:640-654.
4. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544.
5. Jacobson CA, et al. *Lancet Oncol*. 2022;23:91-103.
6. Tully S, et al. *JCO Clin Cancer Inform*. 2019;3:1-9.
7. Dulobdas V, et al. *Blood*. 2023;142(Suppl 1):495.
8. Van de Wiel L, et al. Presented at the 2021 European Society for Blood and Marrow Transplantation Virtual Annual Meeting; March 14-17, 2021. Abstract P017.
9. Van de Wiel L, et al. Presented at the 2023 European Society for Blood and Marrow Transplantation Annual Meeting; April 23-26, 2023; Paris, France. Abstract P198.
10. Alquist L, et al. *Transplant Cell Ther*. 2024;30:S203-S204.
11. Filosto S, et al. *Blood Cancer Discov*. 2024;5:21-33.
12. Locke F, et al. *Blood Adv*. 2020;4:4898-4911.
13. Locke F, et al. *Nat Med*. 2024;30:507-518.

ACKNOWLEDGMENTS

- The patients, families, friends, and caregivers
- All employees of Kite involved over the course of the study for their contributions
- Medical writing support was provided by Edward Sheetz, PhD, of Nexus Global Group Science, funded by Kite
- This study was funded by Kite
- [a] HWS was an employee of Kite when the studies were conducted

DISCLOSURES

- **JRW:** consulting/advisory role for Bristol Myers Squibb, Genentech, and Kite, a Gilead Company; and research funding from ADC Therapeutics, AstraZeneca, Bristol Myers Squibb, Calithera, Genentech, Kite, Kymera, MorphoSys/Incyte, and Novartis.
- Full author disclosures are available through the Quick Response (QR) code

Presented at the 2024 European Hematology Association Annual Congress