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Axicabtagene Ciloleucel Manufacturing Experience From Launch to Present Day: a United States Perspective

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BACKGROUND

- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for relapsed/refractory large B-cell lymphoma (R/R LBCL) after ≥2 lines of systemic therapy and for patients refractory to or who relapsed within 12 months of first-line chemoimmunotherapy[1,2]
  - Axi-cel was approved in second-line (2L) R/R LBCL based on the global Phase 3 ZUMA-7 study (NCT03391466; 77 global sites across 14 countries), which demonstrated superiority of axi-cel versus standard of care (SOC) in event-free survival, response, and overall survival[3,4]
- Axi-cel is administered at over 300 authorized/qualified treatment centers worldwide and is manufactured for commercial use at 3 sites globally (El Segundo, CA, USA; Frederick, MD, USA; and Amsterdam, The Netherlands)
- The axi-cel manufacturing experience for patients in Europe has previously been presented, demonstrating a robust and reliable commercial manufacturing process for these patients[5,6]

Figure 1. Axi-Cel Manufacturing Sites and Authorized Treatment Centers in the United States

Axi-cel, axicabtagene ciloleucel.

- In the United States, axi-cel is manufactured at 3 locations, including 1 site focused on manufacturing axi-cel for clinical development and 2 sites for commercial purposes (**Figure 1**)
- There are currently 137 authorized treatment centers for axi-cel administration in the United States
- Survival outcomes after CAR T-cell therapy in the clinical trial setting are inherently dependent on the manufacturers' ability within the clinical trial to timely provide product for infusion[7]
- Within the real-world setting, timely delivery of axi-cel product may be further impacted by a higher number of patients, a more heterogeneous patient pool, and increasing numbers of manufacturing sites and treatment centers compared with the clinical trial setting
- Consequently, reliable and consistent manufacturing of CAR T-cell products in clinical studies and real-world settings is important for the generalizability of clinical trial findings

OBJECTIVE

- To describe the commercial manufacturing experience for patients with R/R LBCL treated with axi-cel in the United States from launch through May 2023
- To describe the 2L real-world manufacturing experience in the year since approval (April 2022-May 2023) compared with the ZUMA-7 clinical manufacturing experience[3]

METHODS

Data Sources

US Axi-Cel Commercial Manufacturing Experience (2L or later)

- Patients with R/R LBCL registered on KiteKonnect® and leukapheresed for axi-cel manufacturing during a 5.5-year period from November 3, 2017, to May 18, 2023, were included in this analysis; data were extracted as of June 2, 2023

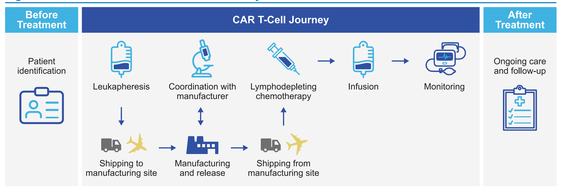
2L Axi-Cel Manufacturing Experience

- 2L Global Clinical Trial Setting: Published data of patients with R/R LBCL randomized to the ZUMA-7 axi-cel arm who underwent leukapheresis (N=178)[3]
- 2L Real-world Clinical Practice in US: Patients with R/R LBCL in 2L registered on KiteKonnect® and leukapheresed between April 8, 2022, and April 7, 2023, were included in the analysis; data were extracted as of May 24, 2023

METHODS *(continued)*

Axi-Cel Treatment Journey

Figure 2. Overview of Axi-Cel Treatment Journey

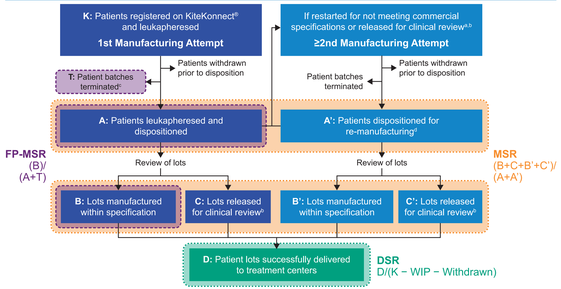


Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor.

- Steps in the axi-cel treatment journey include leukapheresis, manufacturing, and infusion (**Figure 2**)

Manufacturing Terms

Figure 3. Manufacturing and Delivery Success Rate Definitions



First-Pass Manufacturing Success Rate (FP-MSR): Percentage of first-attempt patient lots dispositioned as manufactured within specification (B) out of the total number of first-attempt patient lots dispositioned plus those terminated[c] in the time period (A+T)

Manufacturing Success Rate (MSR): Percentage of those patient lots dispositioned as manufactured within specification or released for clinical review[b] (B+C+B'+C') out of the total number of lots dispositioned in the time period (A+A')

Delivery Success Rate (DSR): Percentage of patient lots shipped (D) out of the total number of patients leukapheresed (excluding those patient lots in process and patients withdrawn; K − WIP − Withdrawn)

[a] Not all patient batches are restarted.
[b] Product that does not meet commercial specification, but is acceptable for clinical specification.
[c] Terminated but not withdrawn.
[d] Majority of processes that are restarted are initiated based on remaining peripheral blood mononuclear cells from previous leukapheresis, and patients do not need to be re-apheresed. Around 1% of patients need to be re-apheresed.
DSR, delivery success rate; FP-MSR, first-pass manufacturing success rate; MSR, manufacturing success rate; WIP, work in progress.

- Metrics used to quantify manufacturing and delivery success in this analysis include manufacturing success rate (MSR), first-pass manufacturing success rate (FP-MSR), and delivery success rate (DSR; **Figure 3**)
- Turnaround time, defined as the time from date of leukapheresis to date of quality release of final product, was also examined
- In cases where lots could not be manufactured for a patient, other manufacturing attempts may be performed
  - In most cases, the subsequent manufacturing attempt was initiated with the remaining peripheral blood mononuclear cells from previous leukapheresis (only ~1% of patients underwent re-apheresis for the following manufacturing attempt)

RESULTS

US Axi-Cel Commercial Manufacturing Experience (2017-2023)

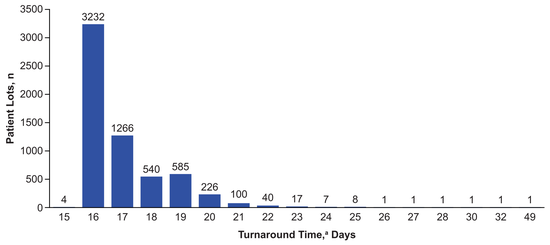
Table 1. Axi-Cel Manufacturing Data for Patients in the United States With R/R LBCL Since Launch

Variables	All Patients
Date range (with final lot disposition available)	November 3, 2017-May 18, 2023
Registered on KiteKonnect® and leukapheresed, N	6665
Delivery success rate, %	97
Manufacturing success rate, %	96
First-pass manufacturing success rate, %	93

Axi-cel, axicabtagene ciloleucel; R/R LBCL, relapsed/refractory large B-cell lymphoma.

- In total, 6665 patients from the United States with R/R LBCL were registered on KiteKonnect® and leukapheresed between November 3, 2017, and May 18, 2023 (**Table 1**)
- A total of 6203 patient lots were delivered to treatment centers, resulting in an MSR of 96%, an FP-MSR of 93%, and a DSR of 97% (**Table 1**)
- The median turnaround time was 16 days (range, 15-49; **Figure 4**)
- Among the 6031 patients analyzed, 99.7% and 75% of patients reported ≤23-day and ≤17-day turnaround times, respectively

Figure 4. Turnaround Times in the Real-World Setting in the United States Since Launch



[a] Turnaround time was defined as the time from date of leukapheresis to date of quality release of final product.

2L Axi-Cel Manufacturing Experience

- Published data from 178 patients from the axi-cel arm of ZUMA-7[3] who underwent leukapheresis were included for comparison with real-world 2L manufacturing outcomes
- Between April 8, 2022, and April 7, 2023, 789 patients with R/R LBCL in the 2L real-world clinical practice setting were registered on KiteKonnect® and leukapheresed

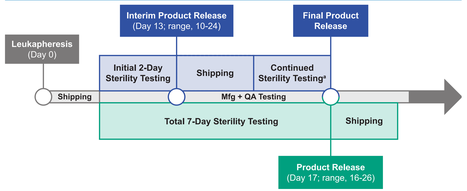
Table 2. Axi-Cel Manufacturing Data for Patients in the United States With R/R LBCL in 2L

Variables	2L Real-World Experience
Date range (with final lot disposition available)	April 8, 2022-April 7, 2023
Registered on KiteKonnect® and leukapheresed, N	789
Manufacturing success rate, %	99
First-pass manufacturing success rate, %	96

2L, second line; axi-cel, axicabtagene ciloleucel; R/R LBCL, relapsed/refractory large B-cell lymphoma.

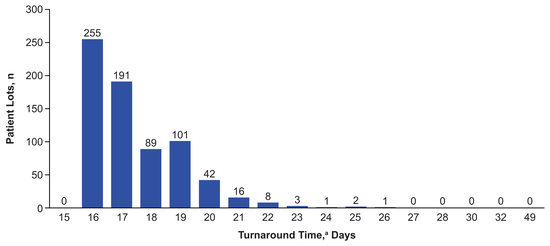
- Axi-cel was successfully manufactured for all patients who underwent leukapheresis in ZUMA-7[3] and in 99% of patients treated in the 2L real-world setting in the United States, with lots dispositioned as quality released or released for clinical review (**Table 2**)
- A 96% FP-MSR was observed in 2L real-world patients in the United States

Figure 5. Manufacturing Process in Clinical Trial (Blue) and Commercial Settings in the US (Green)



[a] Approximately 7 days of sterility testing total.
Mfg, manufacturing; QA, quality assurance; US, United States.

Figure 6. Turnaround Times in the 2L Real-World Setting in the United States



[a] Turnaround time was defined as the time from date of leukapheresis to date of quality release of final product.
2L, second line.

- Differences in median turnaround time for ZUMA-7 versus 2L real-world practice in the United States are to be expected partly due to differences in timing of product shipping in relation to sterility testing and release (**Figure 5**)
  - In ZUMA-7, clinical lots were shipped to treatment sites on interim release based on 2 days of sterility testing results (which was used to calculate turnaround time in prior publications[3]); final product release was completed based on 7-day sterility testing results (**Figure 5**, blue)
  - In real-world practice in the United States, commercial lots were released and shipped to treatment sites only on completion of full release testing (**Figure 5**, green)
- The median turnaround time was 13 days (range, 10-24) for patients who received 2L axi-cel in ZUMA-7 and 17 days (range, 16-26; **Table 2**) for patients who received commercial axi-cel in the 2L real-world setting in the United States, with 96% of product releases in the real-world setting occurring 16-19 days after leukapheresis (**Figure 6**)
- The median time from leukapheresis to axi-cel infusion, or vein-to-vein time (V2VT), in ZUMA-7 (N=170) was 26 days (range, 16-52)[3]
  - A recent real-world analysis demonstrated a median V2VT for axi-cel of 27 days (IQR, 26-32) in the third-line setting for patients with R/R LBCL[8]

CONCLUSIONS

- This analysis demonstrated high overall manufacturing (96%) and delivery (97%) success rates for commercial axi-cel in the United States since launch, and the FP-MSR of 93% is a critical factor in maintaining a timely and dependable manufacturing process
  - This reliability is exemplified by a median turnaround time from leukapheresis to product release of 16 days, with over 99% of patients able to have the final product release within 23 days of leukapheresis
- A supporting analysis of the commercial manufacturing experience for 2L patients with LBCL in the real-world setting showed an MSR consistent with the ZUMA-7 study (99% and 100%, respectively), reinforcing that the robust and rapid manufacturing capability in the clinical trial setting can be replicated in real-world clinical practice
  - V2VT for axi-cel in the 2L clinical trial setting was similar (26-27 days) to the real-world setting in 3L+, suggesting the manufacturing process has been optimized beyond the more controlled context of a clinical trial
- FP-MSR in 2L (96%) was numerically higher than that for all patients since launch (93%), warranting further investigation on potential differences in axi-cel manufacturability across lines of therapy for LBCL
- These results complement the manufacturing experience in Europe,[6] showing consistent, rapid, and reliable manufacturing capabilities in an expanding manufacturing network in 2 key parts of the world
- Efforts are continually ongoing to further optimize the axi-cel manufacturing process and improve delivery times to support optimal patient outcomes
  - For example, the United States Food and Drug Administration recently approved an axi-cel manufacturing process change that is anticipated to reduce median turnaround time by 2 days and further improve the overall manufacturing outcomes of axi-cel[9]

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