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Commercial Manufacturing Experience of Axicabtagene Ciloleucel Delivery in Europe: From the First 2 Years to the Latest 2 Years

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BACKGROUND

- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved in the European Union (EU) on August 28, 2018, for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after ≥2 prior lines of systemic therapy based on the pivotal ZUMA-1 study[1-3]
  - Additionally, on October 17, 2022, axi-cel was approved in the EU for the treatment of adult patients with R/R DLBCL and high-grade B-cell lymphoma that relapses within 12 months of completion of, or is refractory to, first-line chemoimmunotherapy based on the pivotal ZUMA-7 study[1,4]
- In the pivotal Phase 1/2 ZUMA-1 study of axi-cel in patients with R/R LBCL after ≥2 prior lines of therapy, the objective response rate in all patients who received axi-cel (N=101) was 83%, with a complete response rate of 58%[2]
  - Axi-cel was successfully manufactured for 99% of patients and the median time from leukapheresis to product release to the treatment facility was 17 days[3,5]
- In the first 2 years of post-marketing manufacturing experience for European patients with R/R DLBCL, the delivery success rate for axi-cel was 96%, with a median turnaround time of 25 days[6]
- The CAR T-cell therapy manufacturing process should be:
  - Rapid because patients with R/R DLBCL and PMBCL often have aggressive disease and require prompt treatment
  - Robust and reproducible, as patients with prior treatments may be lymphopenic and there may be significant variability in the starting leukapheresis material among patients[7]
  - Reliable to avoid repeat leukapheresis

OBJECTIVE

- Report on the latest 2 years of post-marketing commercial manufacturing experience in Europe (September 6, 2020 to September 5, 2022) for patients who received axi-cel and compare this experience with the manufacturing experience of the first 2 years, as previously reported[6]

METHODS

Manufacturing Terms

- Canceled: order canceled due to patient situation
- Physician's Release: lot did not meet all the release specifications as defined in marketing authorization (MA) but was released under physician's request as defined in EU Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (ATMP) Part IV Section 11.5, Administration of Out of Specification Products
- Qualified Person (QP): The designated, legally bound person who is responsible for lot certification for Investigational and Authorized ATMP lots
- QP Release: lot met all the specifications as defined in MA
- Reject: lot did not meet all the specifications as defined in MA and was rejected for intended use
- Terminate: no dose was produced due to the starting leukapheresis material (eg, insufficient cells to proceed to harvest), contaminated or atypical manufacturing (eg, equipment/hardware malfunction, product leakage, traceability)
- Delivery Success Rate (DSR): The percentage of patients for which a dose was shipped out of the total number of patients leukapheresed in the time period (excluding those patient lots in process and patients withdrawn)
- Manufacturing Success Rate (MSR): percentage of lots QP released or Physician's Released out of the total lots dispositioned in the time period of data extraction (patients' cells classified as in process within the time period of data extraction were excluded)

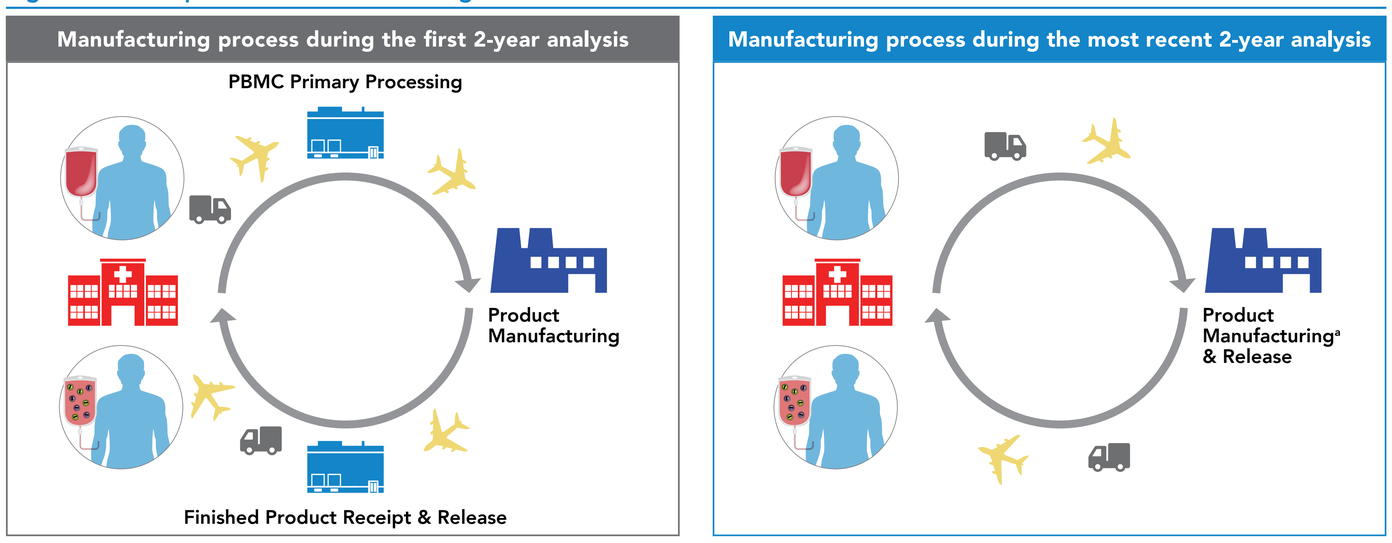
Inclusion criteria

- All axi-cel commercial patients with leukapheresis from EU MA (August 28, 2018) until September 5, 2022
  - This analysis separately analyzes patients leukapheresed from EU MA to September 5, 2020 (first 2 years of data) and September 6, 2020 to September 5, 2022 (latest 2 years of data)
- Manufactured for European countries (including Switzerland and the United Kingdom) and Israel
- Manufacturing process occurred at 1 of 2 sites in either the United States (El Segundo, CA) or the Netherlands (Hoofddorp, The Netherlands; **Figures 1 and 2**)
- Lots that were released, rejected, terminated, or canceled were included

Analyses

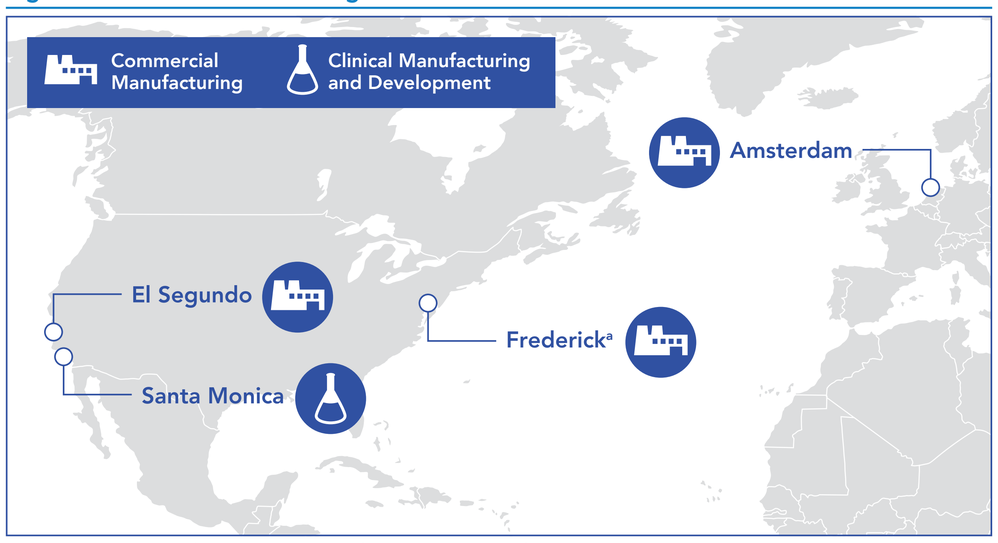
- Manufacturing turnaround time is defined as time from day of leukapheresis to the day of product disposition for lots using fresh apheresis material

Figure 1. EU Shipment and Manufacturing Process



[a] Including PBMC primary processing.
PBMC, peripheral blood mononuclear cell.

Figure 2. Axi-Cel Manufacturing Sites



[a] Frederick, Maryland site not used for EU commercial axi-cel manufacturing in the latest 2 years of data.

RESULTS

- From first leukapheresis after MA, September 6, 2018, until September 5, 2022, 3701 patients from the EU, Great Britain, Switzerland, and Israel were registered on the Kite Konnect® website (the Kite dedicated website portal for cell ordering and ensuring chain of identity and custody) and provided leukapheresis material for axi-cel manufacturing (**Figure 3**)
  - Notably, France has enrolled and leukapheresed almost twice as many patients in the latest 2 years of manufacturing data (648) as it did in the first 2 years of manufacturing data (335)
- From the 2432 patients leukapheresed in the latest 2 years of data 2398 patient lots were shipped to the treatment centers, resulting in a DSR of 99% (**Figure 4**; **Table 1**)
- In total, from the latest 2 years of data, 2449 lots met MA specifications and were QP released or Physician's Released out of 2560 lots dispositioned, resulting in an MSR of 96% (**Figure 4**; **Table 1**)

Figure 3. Patient Origins for First 2 Years and Latest 2 Years of Manufacturing

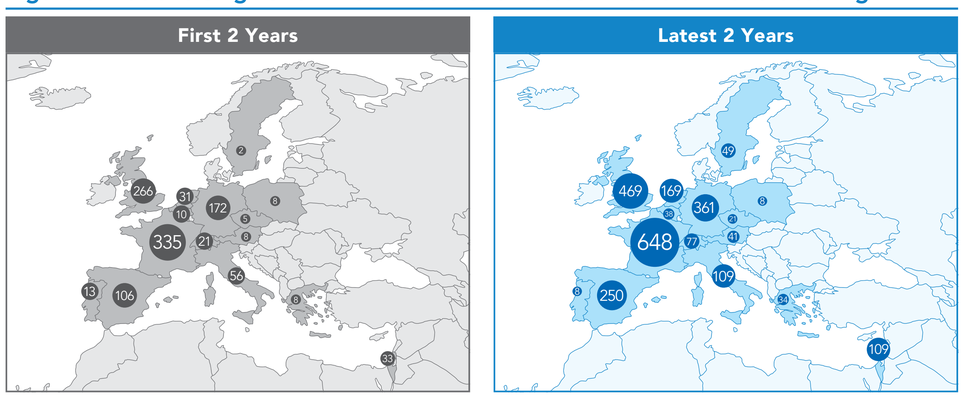
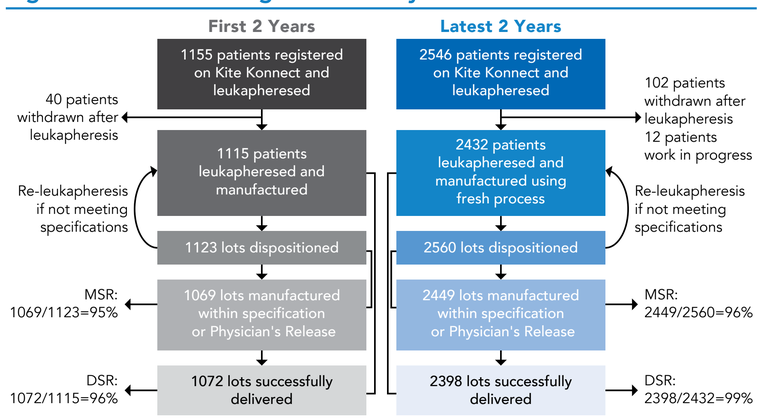


Figure 4. Manufacturing and Delivery Success Rates[a]



[a] Manufacturing data extraction excluded lots that were classified as "in process" within the time period specified, thus the total number of lots at each step may not be representative of every lot dispositioned during the time period.
DSR, delivery success rate; MSR, manufacturing success rate.

Table 1. Manufacturing Comparison of First 2 Years of Manufacturing Experience to Latest 2 Years of Experience

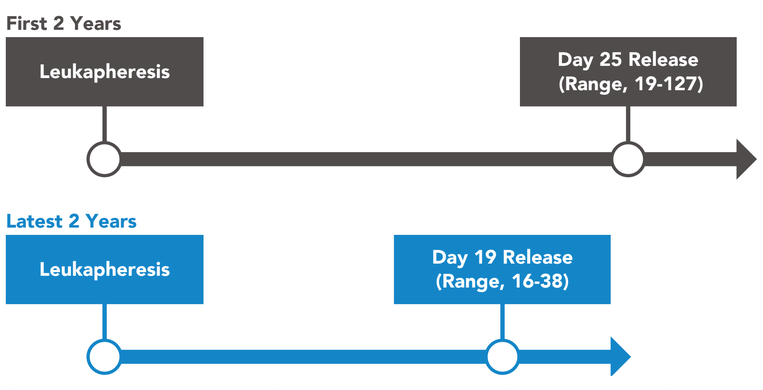
	First 2 years	Latest 2 years
Date range (with final lot disposition available)	September 6, 2018-September 5, 2020	September 6, 2020-September 5, 2022
Patients registered on Kite Konnect® and leukapheresed[a]	1155	2546
Median turnaround time[b] (range), days	25 (19-127)	19 (16-38)
Delivery success rate (n/N lots), %	96% (1072/1115)	99% (2398/2432)
Manufacturing success rate (n/N lots), %	95% (1069/1123)	96% (2449/2560)

[a] Includes patients from the European Union, United Kingdom, Switzerland, and Israel. [b] Based on primary peripheral blood mononuclear cell (PBMC) process. A frozen PBMC process was used in the first 2 years of experience, and a fresh apheresis material process was used in the latest 2 years of experience.

Time From Leukapheresis to Release

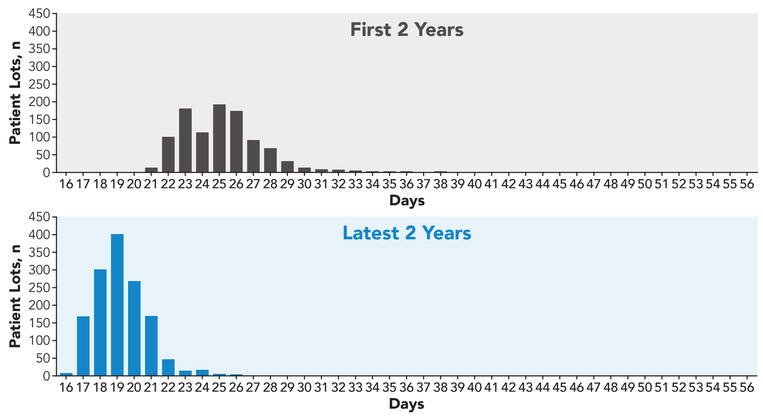
- The median turnaround time from first leukapheresis to QP release from the latest 2 years of data was 19 days (range, 16-38; n=1404; **Figures 5 and 6**)
- By contrast, the median turnaround time from first leukapheresis to QP release from the first 2 years of data was 25 days (range, 19-127; n=1010)

Figure 5. Median Time From Leukapheresis to Release for First 2 Years and Latest 2 Years of Manufacturing



If orders were canceled, rejected, or terminated before release, they did not complete a manufacturing cycle and were therefore not included in the turnaround times.

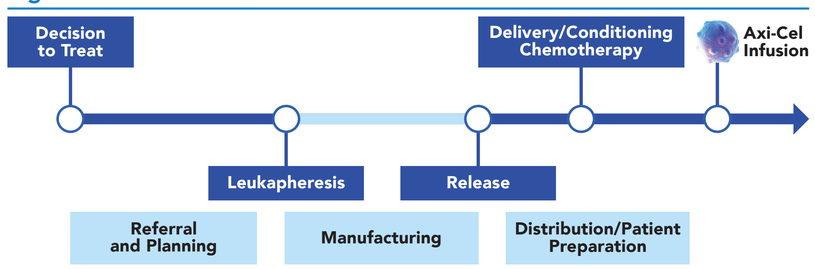
Figure 6. Turnaround Times From Leukapheresis to Release for Lots With 1 Manufacturing Cycle for First 2 Years and Latest 2 Years



DISCUSSION

- Patient outcomes are likely to depend on rapid and reliable manufacturing capability, as real-world experience examining time from leukapheresis to infusion has shown[8]
- Results of the current analysis demonstrate a robust and reproducible commercial manufacturing process with an additional 2 years of data
- Notably, manufacturing and delivery success were not affected by evolution of Kite's manufacturing network, and turnaround times were improved with this increased footprint (**Figure 6**)
- In addition to the manufacturing process examined in this analysis, other factors that contribute to delays in initiating treatment include patient selection, referral processes, and center organization

Figure 7. Treatment Schema



Axi-cel, axicabtagene ciloleucel.

CONCLUSIONS

- Results from the latest 2 years of manufacturing experience demonstrate a consistent and robust commercial manufacturing capability with high success rates (MSR of 96% versus 95% and DSR of 99% versus 96% for latest 2 years versus first 2 years) and improved turnaround times (19 days for latest 2 years versus 25 days for first 2 years) for European patients who received commercial axi-cel
- To further reduce the time from the decision to treat a patient to the infusion of axi-cel, supplementary steps beyond manufacturing are currently being examined for potential optimization (**Figure 7**)
- Axi-cel manufacturing is well-positioned to support the growing patient demand in the EU based on these data

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DISCLOSURES

HWS: employment with and stock or other ownership in Kite, a Gilead Company.

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