BACKGROUND

- Tisagenlecleucel (Kymriah), an autologous CD19-directed CAR-T cell therapy, has been approved by the US Food and Drug Administration for the treatment of:
  - Children and young adults with relapsed/refractory (r/r) acute lymphoblastic leukemia (ALL) (Aug 2017) and
  - Adults with r/r diffuse large B-cell lymphoma (May 2018).
- Post-approval, a key goal has been to upscale and continuously improve manufacturing success and turnaround time in the commercial setting to meet the needs of a global patient population.
- Here, we report accrued experience from our 4-year journey of optimizing the commercial tisagenlecleucel manufacturing process at the US site (Morris Plains, NJ), for faster and successful delivery to patients in the US.

METHODS

- As reported previously, the tisagenlecleucel manufacturing process includes leukapheresis of the patient’s peripheral blood mononuclear cells (PBMCs) and cryopreservation of these (Fig 1).
- This is followed by enrichment and activation of T cells, transduction of the lentiviral vector containing the anti-CD19 CAR-transgene, activation with anti-CD3/CD28 antibody-coated beads, expansion in cell culture, washing, and formulation of the viable cells into a cryopreservation medium (Fig 1).
- The final product is then shipped to the treatment center and infused to patients.

RESULTS

Manufacturing and shipping success rates
- Between Jan-2021 and Aug-2021, at the US manufacturing site, for patients in the US:
  - The manufactured product was available for shipment for 98% of patients (SSR) (Fig 3).
  - The MSR was 96%, with an OOS rate of <3% and no OOS for viability (Fig 3).
  - All the 102 OOS batches were released for infusion as the benefit-risk assessment was positive, including 1 low-dose OOS.
  - Manufacturing was terminated for 2% of patients due to low growth (Fig 3).

Turnaround time
- Throughout 2021, immediate manufacturing capability was available upon the receipt of all apheresis starting material, without waiting time/queues.
  - The median time from the receipt of leukapheresis material at the manufacturing site to shipping (Turnaround time) was 23 days (range, 16–48).
  - The variability in turnaround time decreased over time since 2018 (median 20 days to 12 days in 2021).

Global demand for tisagenlecleucel continues despite the COVID-19 pandemic. As is evident, the pandemic did not appear to have significantly affected the success rate or manufacturing turnaround time.

Manufacturing process improvements
- There were significant improvements from 2018 to 2021 in MSR (99% to 98%), SSR (93% to 99%) and the overall OOS rates (26% to 2%), including viability OOS rate (from 13% to 2%) (Fig 4).
- All the 102 OOS batches were released for infusion as the benefit-risk assessment was positive, including 1 low-dose OOS.
- Manufacturing was terminated for 2% of patients due to low growth.

RESULTS (Cont.)

Manufacturing footprint
- As of Aug-2021, tisagenlecleucel has been manufactured for 5300 patients worldwide, which was enabled by Novartis’s significantly increased global manufacturing footprint.
  - Tisagenlecleucel is commercially manufactured at six different sites that are strategically spread across the globe (US, France, Switzerland, Germany, Japan and Australia).
  - The expansion of manufacturing footprint allowed the increase in capacity in order to meet the patient demand, with immediate manufacturing availability.
  - The global tisagenlecleucel treatment network includes more than 340 certified centers, which includes approximately 131 centers in the US (Fig 2).

Conflicts of interest
All authors are employees of Novartis.

References
4. Modiﬁed T-cell infusion
5. Foundation for Biomedical Research and Innovation, Japan
6. Post-approval, a key goal has been to upscale and continuously improve manufacturing success and turnaround time in the commercial setting to meet the needs of a global patient population.
7. Global demand for tisagenlecleucel continues despite the COVID-19 pandemic. As is evident, the pandemic did not appear to have significantly affected the success rate or manufacturing turnaround time.
8. There were significant improvements from 2018 to 2021 in MSR (99% to 98%), SSR (93% to 99%) and the overall OOS rates (26% to 2%), including viability OOS rate (from 13% to 2%) (Fig 4).
9. All the 102 OOS batches were released for infusion as the benefit-risk assessment was positive, including 1 low-dose OOS.
10. Manufacturing was terminated for 2% of patients due to low growth.
11. Reporting of data from May 2020 onwards when commercial manufacturing of tisagenlecleucel was enabled for both EU and US centers.
12. Acknowledgment
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KEY FINDINGS & CONCLUSIONS

- Continuous investment over the past 4 years has significantly improved manufacturing capacity, turnaround time and quality.
- In 2021, there has been zero queue till date and the median time from the receipt of leukapheresis material at the manufacturing site to shipment was 20 days.
- The MSR has improved significantly from 89% in 2018 to 96% in 2021, and the viability OOS rate has improved significantly from 25% in 2018 to 0% in 2021.
- High manufacturing reliability has been achieved, with the manufactured product available for shipping for 98% of patients.
- The COVID-19 pandemic did not appear to have had an impact on the success rate or manufacturing turnaround time, as evident by the recent success metrics.
- Ongoing process improvements are anticipated to further reduce the throughput time, thereby allowing more patients to have faster access to CAR-T cell therapy.

Figure 1. Tisagenlecleucel manufacturing process

Figure 2. Global commercial manufacturing footprint and certified centers network of tisagenlecleucel

Figure 3. Manufacturing success rate (MSR), shipping success rate (SSR), and out-of-specification (OOS) rate between Jan 2021 and Aug 2021

Figure 4. Evolution of manufacturing success rate (MSR) shipping success rate (SSR) and out-of-specification (OOS) rates from May 2018 to Aug 2021

Figure 5. Tisagenlecleucel manufacturing process improvements

A. Simplified sample preparation for final product (FP) viability testing
B. 5% plasma-derived human AB serum as alternative serum source
C. Expanded cell culture in disposable V-Bags
D. Reduced number of cells processed in final product
E. Sterile disposable protein adsorption columns
F. Polish-derived human AB serum as an alternative serum source

Figure 6. Change to sterile disposable protein adsorption columns due to low growth and higher peak cell counts.

Figure 7. Proportion of patients for whom the manufactured product met the health authority (HA) release criteria out of the total number of patients leukapheresed.

Figure 8. Proportion of patients for whom the manufactured product met the Health Authority (HA) release criteria out of the total number of patients leukapheresed.

Figure 9. Proportion of patients for whom the manufactured product met the Health Authority (HA) release criteria out of the total number of patients leukapheresed.

Figure 10. Proportion of patients for whom the manufactured product met the Health Authority (HA) release criteria out of the total number of patients leukapheresed.

Figure 11. Proportion of patients for whom the manufactured product met the Health Authority (HA) release criteria out of the total number of patients leukapheresed.

Figure 12. Proportion of patients for whom the manufactured product met the Health Authority (HA) release criteria out of the total number of patients leukapheresed.