Optimizing Commercial Manufacturing of Tisagenlecleucel for Patients in the US: A 4-Year Experiential Journey

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Disclosures

• Employee of Novartis.
Introduction

• 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 (Aug-2017); and
  – Adults with r/r diffuse large B-cell lymphoma (May-2018)1

• 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: Tisagenlecleucel manufacturing process

1. LEUKAPHESIS
   - Collection and cryopreservation

2. T-cell TRANSDUCTION
   - with lentiviral vector

3. T-cell EXPANSION

4. Bead removal, FORMULATION, and cryopreservation

5. Chemotherapy

6. ADMINISTRATION
   - Modified T-cell infusion

CD3/CD28 antibody-coated beads for ENRICHMENT and ACTIVATION

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Results

- As of **Aug-2021**, tisagenlecleucel has been manufactured for ~5300 patients worldwide.

- Tisagenlecleucel is commercially manufactured at **6 sites** across the globe.

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

1. Morris Plains, NJ, USA;
2. Les Ulis, France;
3. Stein, Switzerland;
4. Fraunhofer, Germany;
5. Foundation for Biomedical Research and Innovation, Japan;
6. Cell Therapies, Australia
Manufacturing process improvements

- There were significant improvements from 2018 to 2021 in (Figure)
  - MSR (69% to 96%)
  - SSR (93% to 98%)
  - OOS rates (26% to 2%); including viability OOS rate (from 25% to 0%)

Turnaround time is defined as time from the receipt of leukapheresis material at the manufacturing site to shipping

Figure. Evolution of MSR, SSR and OOS rates from May 2018 to Aug 2021
Two key process and analytical improvements were introduced towards the end of 2020:

A. Simplified sample preparation for final product (FP) viability testing

B. 5% plasma-derived human AB serum as alternative serum source

Figure 4. Tisagenlecleucel manufacturing process improvements

5% plasma-derived human AB serum (PDhABs) has been successfully evaluated as an alternative serum and assessed by the FDA for manufacturing.

Previous manufacturing process used off-the-clot (OTC) human AB serum at a concentration of 2%.

Trend toward higher peak cell counts observed with PDhABs.

PDhABs is available in greater supply, to meet anticipated increases in manufacturing demand.
Continuous investment over the past 4 years has significantly improved manufacturing capacity, turnaround time and quality.

The MSR has improved significantly from 69% 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.

MSR, manufacturing success rate; OOS, out-of-specification.