On 28 December 2017, Sattva S. Neelapu of the M.D. Anderson Cancer Center in Houston, Texas and colleagues published in The New England Journal of Medicine, interim results from a phase II study (sponsored by Kite, now a Gilead company, and the Leukemia and Lymphoma Society Therapy Acceleration Program) in patients with refractory large B-Cell lymphoma (LBCL). In this multicenter clinical trial, the safety and efficacy of axicabtagene ciloleucel (axi-cel) was evaluated in patients with diffuse LBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma (FL) who had refractory disease despite undergoing recommended prior therapy (NCT02348216).

The purpose of this study was to determine if this autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy is a safe and effective treatment regimen for these lymphoma-type patients who have received a conditioning regimen of low-dose cyclophosphamide and fludarabine. The primary endpoint was objective response rate (ORR), with secondary endpoints of overall survival (OS), safety, and biomarker assessments.

**Highlights:**

- Axi-cel was associated with durable response in refractory LBCL
- Higher CAR T-cell levels in blood were associated with response

**Treatment:**
A total of N = 111 patients with DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma with refractory disease despite undergoing recommended prior therapy.

Patients received a target dose of $2 \times 10^5$ anti-CD19 CAR T-cells/kilogram body weight after receiving low-dose cyclophosphamide and fludarabine.

Primary endpoint was ORR.

Secondary endpoints included OS, safety, and biomarker assessments.

National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 was used to grade symptoms of cytokine release syndrome and neurologic events, along with other adverse events.

**Efficacy:**

- ORR = 82%, and complete response (CR) rate was 54%
  - 40% continuing to have a CR
  - Median time to response = 1.0 month
  - Median duration of response (DOR) = 8.1 months
- Median overall survival was not reached, 18-month OS rate = 52%
- Median duration of progression-free survival (PFS) = 5.8 months

**Safety:**

- Most common adverse events of grade 3 or higher during treatment were neutropenia (78%), anemia (43%), and thrombocytopenia (38%)
- Grade 3 or higher cytokine release syndrome (CRS) and neurologic events occurred in 13% and 28% of the patients, respectively
- Most common symptoms of CRS grade 3 were pyrexia (11%), hypoxia (9%), and hypotension (9%)
  - 44 patient deaths were reported:
    - disease progression (n=37)
• cytokine release syndrome related to treatment (n=2)
• pulmonary embolism unrelated to treatment (n=1)
• Other causes after disease progression unrelated to treatment (n=4)

In this multicenter study, patients with refractory large B-cell lymphoma who received axi-cel therapy experienced deep and durable responses, with a safety profile that included myelosuppression, the cytokine release syndrome, and neurologic events. It’s important to note that in order to achieve these results, a feasible and reliable CAR T-cell manufacturing protocol and process must be in place. This was clearly demonstrated as axi-cel was manufactured for 110 patients (99%) and administered to 101 of them (91%). What’s more, 82% of the 101 treated patients with refractory LBCL had an objective response, and 54% had a complete response. The authors noted that there may be a limitation with CD19 detection due to the fact that response rates were similar in both CD19-negative and –positive disease. Additionally, they mentioned that an analysis of molecular and cytogenetic characteristics could have been included in the study in order to determine the influence of CAR T-cell therapy outcomes on disease biology.

In consideration of these among many factors and the results of this study, axi-cel was shown to be an effective therapeutic option in adult patients with relapsed or refractory large B-cell lymphoma after at least two prior systemic therapies.

References:

phase-ii-study-in-large-b-cell-lymphoma-axicabtagene-ciloleucel-is-latest-car-t-cell-therapy-to-demonstrate-durable-response