

Highlights in CAR T-Cell Therapy from ASH 2021: Potential Practice-Changing Treatments



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CAR T-cell therapy in DLBCL

Chimeric antigen receptor (CAR) T-cell therapies have revolutionized the treatment of B-cell malignancies, in particular diffuse large B-cell lymphoma (DLBCL). The CD19-targeted, genetically modified autologous T-cell immunotherapies, axicabtagene ciloleucel (axi-cel),¹ and tisagenlecleucel (tisa-cel)² are approved in Switzerland and lisocabtagene maraleucel (liso-cel) is approved by the European Medicines Agency (EMA)³ and Food and Drug Administration (FDA)⁴ for adult patients with relapsed/refractory (R/R) DLBCL after ≥2 lines of systemic therapy. All three use FMC 63 as a single-chain variable fragment (SCVF) to target CD-19. The main difference between these products is the costimulatory domain with CD28 in axi-cel, 4-1BB in tisa-cel and 4-1BB is also employed in liso-cel, alongside CD4 and CD8 in an adjusted number. The approvals were based on 3 pivotal clinical trials ZUMA-1,⁵ JULIET⁶ and TRANSCEND⁷ for axi-cel, tisa-cel and liso-cel, respectively. Progression-free survival (PFS) for the three products was approximately 40% which plateaus over time, suggesting that this approach has curative potential, at least in the third-line. However, this indicates that 60% of patients will ultimately progress, relapse, or will die from their disease. Therefore, generating new products, optimizing existing products and changing the line at which we administer them are all strategies by which we may be able to improve the efficacy of these treatments. Currently, CAR T-cell therapy is approved from the third-line, but this could be altered to the second-line, an approach that is being assessed by three pre-clinical trials: ZUMA-7,⁸ BELINDA⁹ and TRANSFORM.¹⁰ These three trials were randomized, multicenter phase III studies that included patients with R/R DLBCL, with relapses occurring within 12 months from the first-line therapy. This high-risk population was randomized to receive CAR T cells or standard of care (SOC), which was second-line chemotherapy. Platinum-based chemotherapy was used in the majority of cases for 2–3 cycles. Depending on the response, patients with complete

response (CR) or partial response (PR), would undergo high-dose chemotherapy and autologous stem cell transplantation (ASCT) when eligible. In patients with stable or progressive disease, third-line ASCT consolidation was employed.

ZUMA-7 trial met its primary endpoint of event-free survival

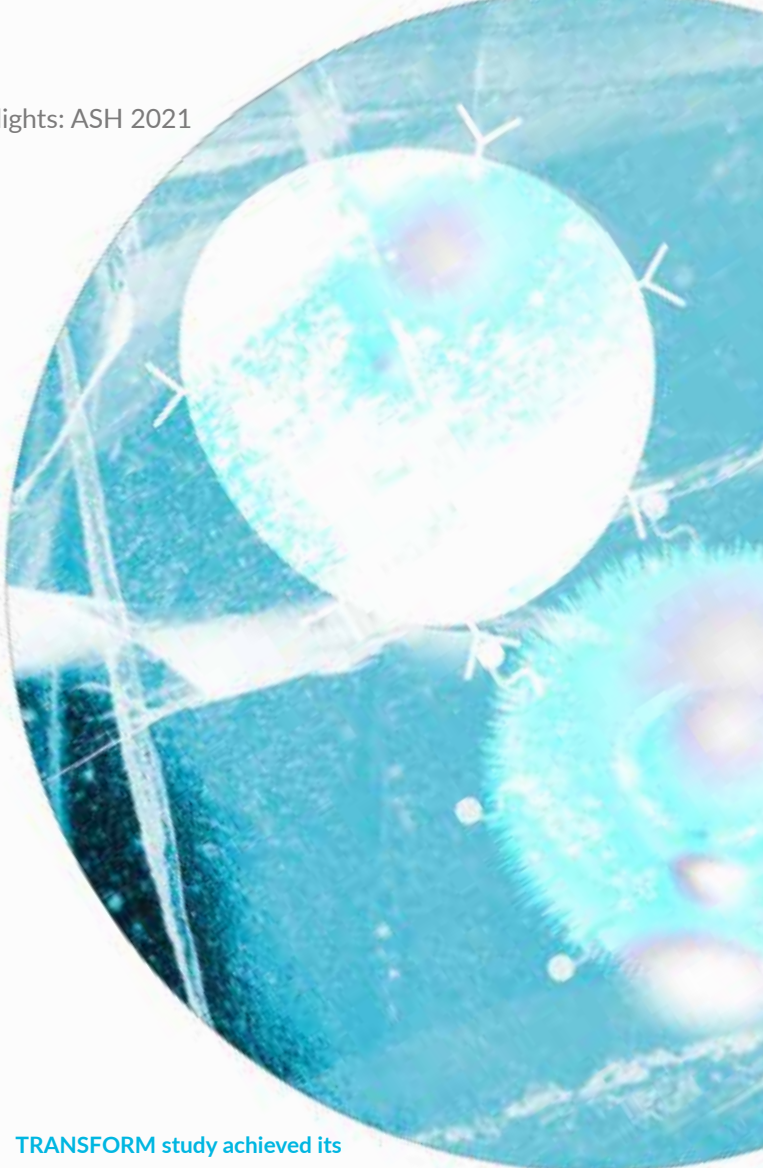
Dr Frederick Locke presented the primary analysis of the ZUMA-7 trial, which evaluated the safety and efficacy of axi-cel in a head-to-head study against SOC for the treatment of adult patients with large B-cell lymphoma (LBCL) at the plenary session of ASH 2021.¹¹ This multicenter trial included 359 adult patients with LBCL who relapsed or were refractory to the first-line treatment. Furthermore, all patients were required to be eligible for ASCT. Patients were randomized 1:1 to either axi-cel or the SOC (platinum-based chemotherapy for 2–3 cycles) treatment arms. The primary endpoint was event-free survival (EFS). The majority of patients received axi-cel therapy (94%), while a little more than a third of patients (36%) in the SOC arm actually received ASCT. Axi-cel was associated with a statistically significantly 4-fold greater median EFS compared with the SOC arm (8.3 months vs 2.0 months; HR: 0.398 [95% CI: 0.308–0.514]; p<0.0001). This clear and significant difference is supported by the 2-year EFS, axi-cel demonstrated a 2.5-fold increase in the proportion of patients who were alive and did not require the need for additional cancer treatment or experienced cancer progression (40.5% vs 16.3%). This is also reflected in the overall response rate (ORR) for the two groups, which was 83% in the axi-cel group, compared with 50% in the SOC group, as well as 2/3 of patients and 1/3 of patients, respectively adopting a complete response. In the interim overall survival (OS) data, there is a potentially significant difference between the two arms with a slightly improved OS for the axi-cel group compared with the SOC. However, 56% of patients in the SOC group crossed over to receive CAR T cells, which was not taken into account for the OS data.

BELINDA trial shows no significant difference between tisa-cel and standard of care

The open-label, multicenter, phase III BELINDA trial investigated the efficacy and safety of tisa-cel versus SOC in adult patients with R/R aggressive B-cell non-Hodgkin's lymphoma (NHL) within 12 months of first-line therapy.¹² A major differing component between the BELINDA and ZUMA-7 trials was that bridging chemotherapy was allowed in the former trial; whereas in ZUMA-7, patients directly received CAR T cells and were not allowed to receive chemotherapy. In the BELINDA trial, investigators were free to employ chemotherapy as needed in the tisa-cel arm and SOC arm. Crossover was permitted between the two arms, while the primary endpoint of EFS was defined as stable/progressive disease by evaluation at 12 weeks after inclusion or death at any time. A total of 322 patients were randomized 1:1 to tisa-cel (n=162; Arm A) or SOC (n=160; Arm B). About 96% of the patients in the tisa-cel group received the treatment, while in the SOC group, 33% of patients received ASCT. This low proportion is likely due to the fact that 81% of patients crossed over to receive CAR T-cell treatment following an insufficient response to chemotherapy. Baseline demographic and disease characteristics were similar between the two arms, with the only major difference being that hybrid lymphoma with *BCL2* or *BCL6* rearrangement was represented in the tisa-cel arm significantly higher than the SOC arm. It is important to note that the median time to infusion for all patients in the tisa-cel arm was 52 days. Investigators had discussed the difference between US and the non-US centers, which was significant since the median time to infusion for US centers was 41 days, while it was almost two months for non-US centers. The median EFS was identical between the 2 arms (3.0 months; HR: 1.07 [95% CI: 0.82–1.40]; p=0.69). Furthermore, ORR data was very similar in the tisa-cel and SOC arms (56% vs 52%), while CR was also the same between the two arms (28.4% vs 27.5%).

TRANSFORM study achieved its primary endpoint of event-free survival

The phase III TRANSFORM study investigated the efficacy and safety of liso-cel in the second-line treatment of patients with R/R LBCL.¹⁰ Similar to the TRANSCEND study, which led to liso-cel approval, more histological types were included in the TRANSFORM trial. A total of 184 patients underwent 1:1 randomization to either the SOC or liso-cel treatment arms. Bridging therapy was lowered up to 1 cycle for the liso-cel treated arm, while the SOC arm required no bridging therapy. The primary endpoint of the trial was EFS which was defined as the time from randomization to death of any cause, progressive disease and failure to achieve CR or PR by 9 weeks post-randomization or start of a new anti-neoplastic therapy. A higher proportion of patients received liso-cel in the treatment arm (97%), while in the SOC group, nearly 46% of patients received ASCT. This study had a median follow-up of just 6.2 months; therefore, the data are less mature than the ZUMA-7 or BELINDA trials. A statistically significant improvement in EFS, with a median EFS of 10.1 months in the liso-cel arm, compared with 2.3 months in the SOC arm. While this is statistically significant, there is not enough data to determine long-term survival. ORR was significantly higher in the liso-cel arm compared to the SOC, especially for complete remission. OS was the secondary endpoint of the study, but the data was not mature enough to evaluate. The primary analysis showed a potentially statistically significant difference between the liso-cel group and the SOC group.



Collective result of CAR T-cell trials

From the three trials, ZUMA-7 and TRANSFORM met their respective primary endpoints which the BELINDA trial failed to achieve. ORR data and CR improvement suggest CAR T-cell treatment superiority compared with SOC. This was certainly similar in the ZUMA-7 and TRANSFORM study; however, no difference was observed in the BELINDA study. The median EFS in the SOC group was similar between the three studies: 2 months, 3 months and 3 months in ZUMA-7, BELINDA and TRANSFORM, respectively. However, only ZUMA-7 and TRANSFORM showed an improved median EFS of 8.3 and 10.1 months, respectively.

Possible causes for the disparity between ZUM-7, BELINDA and TRANSFORM

There are ongoing discussions regarding the reason for the disparity in the BELINDA compared with ZUMA-7 and TRANSFORM. The difference in results may have been due to a varying definition of EFS. Bridging was not allowed in the ZUMA-7 trial, while BELINDA and TRANSFORM permitted bridging treatment. The BELINDA trial allowed more freedom to the investigator to use bridging as needed. This may have impacted the time to infusion. Patients in the ZUMA-7 study waited

29 days from inclusion to infusion,¹¹ which was significantly shorter than the BELINDA trial which was 52 days.¹² Furthermore, clinical practice employed for third-line lymphodepleting chemotherapy regimens are different for axi-cel, tisa-cel and liso-cel, with the highest doses of cyclophosphamide being administered for axi-cel and the lowest for tisa-cel.

Are these results practice-changing?

The most critical question facing physicians now is: Is CAR T-cell therapy the new SOC in second-line R/R DLBCL? While the data may be promising, several aspects must be taken into account, especially as the data is still fresh. Results of these trials are based on EFS, which were very different between them. Whether these results will reflect an impact on OS is not known yet as the data are still not mature. The eligibility criteria for the 3 trials were specified only for patients with R/R disease with relapses occurring <12 months when including clinical trials. Geographical location also has an impact, as shown by the difference in time to infusion, with patients in the US with a significant advantage. Furthermore, the bridging strategy was different between the ZUMA-7 and BELINDA study. An optimal bridging strategy has to be defined and kept in mind for patients in the second-line.

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