Second-line Treatment With CAR T-Cell Therapy for Large B-Cell Lymphoma

Forat Lutfi, MD,[1] Ameet Patel, MD,[2] Jasmine Mehta, BS,[3] Anmol Goyal, MD,[3] and Saurabh Dahiya, MD[4]

[1]Hematologic Malignancies and Cellular Therapeutics, The University of Kansas Medical Center, Kansas City, Kansas

[2]Oncology Hematology Care, Cincinnati, Ohio

[3]Stanford Healthcare, Stanford, California

[4]Blood and Marrow Transplantation and Cellular Therapy, Stanford University, Stanford, California

Corresponding author:
Forat Lutfi, MD
The University of Kansas
KU Medical Center
3901 Rainbow Boulevard
Kansas City, KS 66160
Email: flutfi@kumc.edu

Abstract: The landscape for the treatment of patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) has continued to evolve. However, challenges continue to exist, particularly in patients who do not respond to first-line anti-CD20 monoclonal antibody and anthracycline-based therapy or those who experience early relapse. In such patients, the treatment paradigm has changed little in the past 2 decades, with salvage chemotherapy followed by myeloablative chemotherapy and autologous hematopoietic stem cell transplant resulting in historical durable response rates of approximately 40%. Given the success of chimeric antigen receptor (CAR) T-cell therapy in the third- or later-line in the R/R LBCL setting, 3 recent clinical trials (ZUMA-7, BELINDA, and TRANSFORM) have sought to address the clinical need for improved therapies in the high-risk second-line setting for primary R/R disease in the first 12 months. In this review, we analyze these 3 pivotal trials with a focus on clinical trial design, CAR T-cell product attributes, efficacy data, safety data, and patient-reported outcomes when compared with standard of care.

Keywords
Axicabtagene ciloleucel, CAR T-cell therapy, large B-cell lymphoma, lisocabtagene maraleucel, tisagenlecleucel

Introduction

Relapsed or refractory (R/R) large B-cell lymphoma (LBCL) has historically been a therapeutic challenge. As demonstrated in the SCHOLAR-1 study, standard-of-care (SOC) chemoimmunotherapy in refractory LBCL produces an objective response rate of 26% and a median overall survival (OS) of 6.3 months.[1] These dismal findings are further supported by previous studies.[2,3] For 3 decades, the SOC for this patient population has been salvage chemotherapy followed by high-dose chemotherapy and consolidative autologous hematopoietic stem cell transplant (auto-HSCT). This approach

Table 1. Highlights of Trial Designs and Outcomes

CAR T-Cell/SOC	ZUMA-7[12] (axi-cel)	BELINDA[13] (tisa-cel)	TRANSFORM[14] (liso-cel)
Total enrolled (**CAR T-cell**/SOC)	**180**/179	**162**/160	**92**/92
Received bridging	36% (glucocorticoids only)	**83%**	**56%**
≥Stage III disease (**CAR T-cell**/SOC)	**77%**/82%	**66%**/61%	**74%**/68%
Median follow-up, mo	24.9	10.0	6.2
Randomization to infusion time of CAR T-cell, d	29	52	36
EFS, 95% CI, mo (**CAR T-cell**/SOC)	**8.3 (4.5-15.8)**/2 (1.6-2.8)	**3.0 (2.9-4.2)**/3.0 (2.9-4.2)	**10.1 (6.1-NR)**/2.3 (2.2-4.3)
ORR (**CAR T-cell**/SOC)	**83%**/50%	**38%**/43%	**86%**/48%
Median PFS, mo (95% CI) (**CAR T-cell**/SOC)	**14.7 (5.4-could not be estimated)**/3.7 (2.9-5.3)	Not reported	**14.8 (6.6-NR)**/5.7 (3.9-9.4)
FDA approval for CAR T-cell in second line, label indication	Yes, in LBCL refractory to first-line therapy or that relapses within 12 mo of first-line therapy	No	Yes, LBCL, high-grade BCL, PMBCL, and FL grade 3B that is refractory to first-line therapy or that relapses within 12 mo of first-line CIT
NCCN recommendation	Same as FDA	No	Same as FDA, plus disease refractory to first-line therapy or that relapses after first-line CIT in patients who are not eligible for transplant owing to comorbidities or age[a]

[a]NCCN recommendation per phase 2 PILOT study.

axi-cel, axicabtagene ciloleucel; BCL, B-cell lymphoma; CAR, chimeric antigen receptor; CIT, chemoimmunotherapy; d, days; EFS, event-free survival; FDA, US Food and Drug Administration; FL, follicular lymphoma; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; mo, months; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphoma; SOC, standard of care; tisa-cel, tisagenlecleucel.

leads to remission in approximately 40% of patients and a 5-year OS rate of approximately 50%.[4,5] Outcomes have been significantly worse in the primary refractory and early relapse (<12 months) setting, where disease is often chemorefractory to at least some degree and response rates are only half those of patients with a later relapse.[3,6]

The introduction of chimeric antigen receptor (CAR) T-cell therapy, with initial US Food and Drug Administration (FDA) approval in 2017 of axicabtagene ciloleucel (axi-cel; Yescarta, Kite) and tisagenlecleucel (tisa-cel; Kymriah, Novartis) in the third- or later-line R/R setting, has significantly improved outcomes in this high-risk patient group. Overall response rates (ORRs) are 50% to 80%, and durable response rates at 5 years among those with an initial complete response are approximately 60%.[7-10] For patients with primary refractory or early relapsed disease in the second line, however, there remains an unfilled clinical need for therapies with alternative mechanisms of action to improve patient outcomes. There is additional concern that further lines of chemoimmunotherapy in such patients may lead to decreased fitness, and that subsequent disease progression will result in a higher burden of disease prior to qualifying for CAR T-cell therapy.

Given the success of CAR T-cell therapy to date, many in the field have hypothesized that the use of CAR T-cell therapy earlier in the second line, particularly in chemorefractory patient populations that are at especially high risk, may improve the current dismal outcomes. This has been a hotly debated topic with few real-world data. Using the Center for International Blood and Marrow Transplant Research registry, Shadman and colleagues retrospectively compared CAR T-cell vs SOC therapy in patients with radiographic evidence of a partial response (PR) prior to either, and did not find a significant difference between the 2 approaches in 2-year progression-free survival (PFS) or 100-day nonrelapse mortality.[11] However, there was a significantly lower incidence of relapse/progression in the auto-HSCT group vs the CAR T-cell group, at 40% vs 53%, respectively. Two-year OS also was superior in the auto-HSCT group vs the CAR T-cell group, at 69%

vs 47%. In subgroup analysis of primary refractory and early relapse disease, there was no significant difference in 2-year PFS between the 2 groups, but the auto-HSCT group had significantly lower relapse/progression rates (38% vs 56%) and superior 2-year OS (66% vs 40%) compared with the CAR T-cell group. Although retrospective, this study has led many to wonder if CAR T-cell therapy should be considered prior to auto-HSCT, given the seemingly inferior outcomes of CAR T-cell therapy. Of note, these patients were in PR and, by definition, had disease that was refractory to anthracycline-based therapy but not to salvage chemotherapy or high-dose chemotherapy. Furthermore, this was a comparison with CAR T-cell therapy in the third line (the median number of lines of therapy in the CAR T-cell group was 3; range 2-11).

Nonetheless, there has remained an unmet need in patients with especially high-risk, chemorefractory, primary refractory, and early-relapse LBCL, beyond the conventional salvage chemotherapy followed by high-dose chemotherapy and auto-HSCT.

Herein, we review the 3 landmark clinical trials (ZUMA-7, BELINDA, and TRANSFORM) exploring second-line use of CAR T-cell therapy compared with SOC therapy in the primary refractory and early-relapse setting for LBCL. The results of all 3 trials have appeared in peer-reviewed publications.[12-14]

We further explore the similarities and differences among these trials in terms of study design, study population, disease characteristics, CAR T-cell manufacture and administration, cell dosing, kinetics, and expansion, as well as toxicities, response/efficacy, and with SOC comparators. Patient-reported outcomes (PROs) are also explored. The objective of this review is to comprehensively discuss the information captured individually and collectively by these 3 trials, although we avoid making definitive conclusions (See Table 1 for a high-yield summary of cross-trial comparisons).

Trial Design

All trials were multinational with clinical sites in North America, Europe, and Asia in adults aged 18 years and older with confirmed LBCL that was primary refractory or had early relapse within 12 months of first-line therapy with an anthracycline and anti-CD20 monoclonal antibody. BELINDA had the most international trial participants by far.

CAR T-Cell Therapy Arms

ZUMA-7. Of 180 patients enrolled in the CAR T-cell arm of ZUMA-2, 94% received CAR T-cell infusion (see Table 2). The only bridging therapy permitted was glucocorticoids, which 36% of patients received. The median time from randomization to infusion was 29 days. The target CAR T-cell dose was weight based, with 1.4×10^8 cells for a 70-kg patient and the time to peak CAR T-cell level occurring at 7 days. No cases of CAR T-cell cell manufacturing failure occurred.

The median age of those receiving CAR T-cell therapy was 58 years, with 28% being 65 years or older, 61% being male, and 81% being White (see Table 3). Most patients (77%) had stage III or higher disease, with 74% of disease being primary refractory. Those with central nervous system (CNS) involvement were excluded from the trial.

At a median follow-up of 25 months, event-free survival (EFS) was 8.3 (95% CI, 4.5-15.8) months, PFS was 14.7 (95% CI, 5.4 to could not be estimated) months, and the hazard ratio (HR) for an event in the CAR T-cell therapy vs SOC arms was 0.5 (95% CI, 0.31-0.51; see Table 4). The response rate was 83%, with 65% of patients achieving a best overall response of complete response.

All patients experienced an adverse event (AE), with 91% of patients experiencing a grade 3 or higher AE (see Table 5). Neutropenia occurred in 71% of patients. Any-grade cytokine release syndrome (CRS) occurred in 92% of patients, with 6% experience grade 3 or higher CRS. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 60% of patients, and 21% experienced grade 3 or higher ICANS. There was 1 CAR T-cell–related death.

BELINDA. Of 162 patients enrolled in the CAR T-cell arm of BELINDA, 96% received CAR T-cell infusion. Bridging therapy was used in 83% of patients. The median time from randomization to infusion was 52 days (40 days for US sites and 54 days for non-US sites). The median CAR T-cell dose was 2.9×10^8 cells, with a time to peak CAR T-cell level occurring at 14 days.

The median age of those receiving CAR T-cell therapy was 59.5 years, with 33% of patients being 65 years of age or older, 64% being male, and 79% being White. Most patients (66%) had stage III or higher disease, with 66% being primary refractory. A history of secondary CNS disease was permitted if it had been treated previously.

At a median follow-up of 10 months, the EFS was 3 (95% CI, 2.9-4.2) months, and the HR for an event in the CAR T-cell vs SOC arms was 0.95 (95% CI, 0.72-1.25). The response rate was 51% with 28% of patients achieving a best overall response of complete response.

Nearly all patients experienced an AE, with 84% experiencing grade 3 or higher. Neutropenia occurred in 41% of patients. Any-grade CRS occurred in 61% of patients, with 5% experiencing grade 3 or higher CRS. ICANS occurred in 10% of patients, and 2% of patients experienced grade 3 or higher ICANS. There were 4 CAR T-cell–related deaths.

Table 2. CAR T-Cell Product and Trial Design, Manufacture, and Follow-up

Trial	ZUMA-7[12] (n=180)	BELINDA[13] (n=162)	TRANSFORM[14] (n=92)
Product	Axi-cel	Tisa-cel	Liso-cel
Number receiving CAR T-cell therapy	170 (94%)	155 (95.7%)	90 (97.8%)
Tumor CD19-positive by IHC or flow cytometry	144 (80%)	Not reported	
Bridging permitted	Yes, glucocorticoids only	Yes	Yes
Bridging received	65 (36%)	135 (83%)	58 (63%)
Lymphodepleting regimen	Flu 30 mg/m^2 × 3 d; Cy 500 mg/m^2 × 3 d	Flu 25 mg/m^2 × 3 d; Cy 250 mg/m^2 × 3 d	Flu 30 mg/m^2 × 3 d; Cy 300 mg/m^2 × 3 d
CD4:CD8 CAR selection	None	None	1:1
Target CAR dose	2 × 10^6 cells/kg (1.4 × 10^8 cells)[a]	0.6-6.0 × 10^8 (median, 2.9 × 10^8) cells	1.0 × 10^8 cells
Time to peak CAR T-cell level, median (range)	7 (2-233) d	14 (7-42) d[b]	10 (6-22) d
Median peak CAR T-cell level	25.84 cells/mm^3	Not reported	33349 copies/μg
CAR T-cell manufacturing failure	0	Not reached	1 (1.1%)
Median randomization to infusion time, d	29	52 (40 US, 54 non-US)	36
Median follow-up time, mo	24.9	10	6.2

[a]Estimated total CAR dose based on a 70-kg patient

[b]Actual values not reported; this value is based on Figure S9 in Gisselbrecht C et al. *J Clin Oncol*. 2010;28(27):4184-4190.[3]

CAR, chimeric antigen receptor, Cy, cyclophosphamide; d, days; Flu, fludarabine; IHC, immunohistochemistry; mo, months.

TRANSFORM. Of 92 patients enrolled in the CAR T-cell arm, 98% received CAR T-cell infusion. Bridging therapy was used in 63% of patients. The median time from randomization to infusion was 36 days. The target CAR T-cell dose was 1.0 × 10^8 cells, with the time to peak CAR T-cell level occurring at 10 days. There was 1 case of CAR T-cell cell manufacturing failure.

The median age of those receiving CAR T-cell therapy was 60 years, with 39% of patients being 65 years or older, 48% being male, and 59% being White. Most patients (74%) had stage III or higher disease, with 73% of disease being primary refractory. Secondary CNS disease was permitted in the trial.

At a median follow-up time of 6 months, EFS was 10.1 (95% CI, 6.1 to not reached [NR]) months, PFS was 14.8 (95% CI, 6.6 to NR) months, and the HR for an event in the CAR T-cell therapy vs SOC arms was 0.35 (95% CI, 0.23-0.53). The response rate was 86%, with 66% of patients achieving a best overall response of complete response.

All patients experienced an AE, and 92% experienced grade 3 or higher. Neutropenia occurred in 82% of patients. Any-grade CRS occurred in 49% of patients, with 1% being grade 3 or higher. ICANS occurred in 12% of patients, with 4% of patients experiencing grade 3 or higher ICANS. There was 1 CAR T-cell–related death.

Standard-of-Care Arms

The SOC arms in each trial, where reported, had comparable median age, sex, Eastern Cooperative Oncology Group performance status, and treatment characteristics, which were also similar to the CAR T-cell arms (see Table 3).

The ZUMA-7 SOC arm received 2 or 3 cycles of salvage chemotherapy (R-GDP, R-DHAP, R-ICE, or R-ESHAP), and those with a partial or complete response proceeded to high-dose chemotherapy and auto-HSCT. In BELINDA, the SOC arm received salvage chemotherapy (R-GDP, R-DHAP, R-ICE, or R-GemOx), with 97% receiving 2 or more cycles followed by high-dose chemotherapy and auto-HSCT. In TRANSFORM, 3 cycles of salvage chemotherapy (R-DHAP, R-ICE, or R-GDP) were given followed by high-dose chemotherapy and auto-HSCT.

Response rates to salvage chemotherapy were higher than historically reported values (45% in ZUMA-7, 51%

Table 3. Patient and Disease Characteristics, CAR T-Cell Therapy vs SOC

CAR T-Cell/SOC	ZUMA-7[12] **(n=180)**/(n=179)	BELINDA[13] **(n=162)**/(n=160)	TRANSFORM[14] **(n=92)**/(n=92)
Age, median (range)	**58 (21-80)**/60 (26-81) y	**59.5 (19-79)**/58 (19-77) y	**60 (20-74)**/58 (42-65)[a] y
≥65 y	**51 (28%)**/58 (32%)	**54 (33.3%)**/46 (28.8%)	**36 (39%)**/25 (27%)
Male	**110 (61%)**/127 (71%)	**103 (63.6%)**/98 (61%)	**44 (48%)**/61 (66%)
Race/ethnicity			
Asian	**12 (7%)**/10 (6%)	**20 (12.3%)**/22 (13.8%)	**10 (11%)**/8 (9%)
Black	**11 (6%)**/7 (4%)	**8 (4.9%)**/3 (1.9%)	**4 (4%)**/3 (3%)
White	**145 (81%)**/152 (84%)	**128 (79%)**/128 (80%)	**54 (59%)**/55 (60%)
All others	**12 (7%)**/10 (6%)	**6 (3.7%)**/7 (4.4%)	**24 (26%)**/26 (28%)
ECOG of 1	**85 (47%)**/79 (44%)	**70 (43.2%)**/65 (41%)	**44 (48%)**/35 (38%)
Disease stage ≥III	**139 (77%)**/146 (82%)	**107 (66%)**/98 (61%)	**68 (74%)**/63 (68%)
IPI ≥2[a]	**82 (46%)**/79 (44%)	**106 (65.4%)**/92 (58%)	**36 (39%)**/37 (40%)
Cell of origin			
Germinal center B-cell-like	**109 (61%)**/99 (55%)	**46 (28.4%)**/63 (39.4%)	**45 (49%)**/40 (43%)
Activated B-cell-like	**16 (9%)**/9 (5%)	**52 (32.1%)**/42 (26.2%)	**21 (23%)**/29 (32%)
All others	**55 (30%)**/71 (40%)	**64 (39.5%)**/55 (34.4%)	**26 (28%)**/23 (25%)
Primary refractory disease	**133 (74%)**/131 (73%)	**107 (66%)**/107 (67%)	**67 (73%)**/68 (74%)
Disease relapse <12 mo	**47 (26%)**/48 (27%)	**55 (34%)**/53 (33%)	**25 (27%)**/24 (26%)
Rearrangement of *MYC* with rearrangement of *BCL2*, *BCL6*, or both	**31 (17%)**/25 (14%)	**32 (19.8%)**/19 (11.9%)	**22 (24%)**/21 (23%)
Bone marrow involvement	**17 (9%)**/15 (8%)	Not reported	**9 (10%)**/13 (14%)
Elevated LDH[b]	**101 (56%)**/94 (53%)	Not reported	**10 (11%)**/11 (12%)
Tumor burden	**2123 (181-22538)**/2069 (252-20117)[c]	Not reported	**1140 (530-3500)**/1570 (1040-3080)[d]

[a]Age-adjusted IPI utilized for ZUMA-7 and TRANSFORM, IPI utilized in BELINDA

[b]Elevated LDH defined in ZUMA-7 as greater than the upper limit of normal of local laboratory while TRANSFORM used a value of ≥500 U/L

[c]Median tumor burden in terms of mm2 (range)

[d]SPD, sum of the product of perpendicular diameters in mm^2 (range)

CAR, chimeric antigen receptor; ECOG, Eastern Cooperative Oncology Group prognostic score; IPI, International Prognostic Index; LDH, lactate dehydrogenase; mo, months; SOC, standard of care; y, years.

in BELINDA, and 48% in TRANSFORM; see Table 3). Approximately one-third of patients proceeded to high-dose chemotherapy and auto-HSCT in ZUMA-7 and BELINDA, as did 46% of those in TRANSFORM. EFS in the SOC group was 2 months in ZUMA-7 and TRANSFORM, and 3 months in BELINDA.

Crossover to CAR T-cell therapy was not planned in ZUMA-7, but was permitted in those whose disease failed to respond to SOC therapy. In BELINDA, crossover was permitted at or beyond the week 12 assessment if progressive disease or stable disease occurred. In TRANSFORM, crossover was permitted in cases of failure to respond to SOC therapy at 9 weeks after randomization, progressive disease at any time, or the start of new antineoplastic therapy after auto-HSCT. In all trials, crossover to CAR T-cell in the SOC arm occurred in just over half of patients.

EFS was significantly and dramatically lower in the SOC arms than the CAR T-cell arms in ZUMA-7 (2 vs 8.3 months) and TRANSFORM (2.3 vs 10.1 months). However, in BELINDA, EFS in the SOC arm was longer than in the other trials, and there was no significant difference in EFS between the SOC and CAR T-cell arms (3 months in both). Median PFS was notably longer for CAR T-cell vs SOC therapy in both ZUMA-7 (14.7 vs 3.7

months) and TRANSFORM (14.8 vs 5.7 months), and was not reported in BELINDA. The best overall response of complete response occurred at a much higher rate with CAR T-cell therapy vs SOC therapy in both ZUMA-7 (65% vs 32%) and TRANSFORM (66% vs 39%), and was comparable in BELINDA (28.4% vs 28%). The HR for an event in the CAR T-cell therapy vs SOC arms favored CAR T-cell therapy in both ZUMA-7 (HR, 0.5; 95% CI, 0.31-0.51) and BELINDA (HR, 0.35; 95% CI, 0.23-0.53), but not in TRANSFORM (HR, 0.95; 95% CI, 0.72-1.25).

Patient-Reported Outcomes

Given that patients have a high occurrence of adverse events that affect overall quality of life (QOL), PROs are an extremely important factor that may often be overlooked in trial assessment. PROs have been reported in abstract form at the 2021 American Society of Hematology symposium for ZUMA-7 and TRANSFORM. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was used in both trials.[15] Additionally, ZUMA-7 used the EuroQol Foundation 5-dimension, 5-level visual analogue scale (EQ-5D-5L-VAS) questionnaire, and TRANSFORM used the Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) questionnaire.[16]

In ZUMA-7, the EORTC QLQ-C30 and EQ-5D-5L-VAS were measured at baseline, day 50, day 100, day 150, month 9, and every 3 months up to 24 months or once an EFS event occurred. Participation was high, with 92% in the CAR T-cell arm and 73% in the SOC included in PRO analysis.[17] There was a significant difference in mean change of physical functioning score from baseline to day 100 in favor of CAR T-cell therapy. However, this was not significant at later times. The mean change in score on the global health status/QOL and EQ-5D-5L-VAS also favored axi-cel at days 100 and 150, although this was not significant at later times. However, given higher attrition rates in the SOC arm, the number of patients at later times was lower than in the CAR T-cell arm.

In TRANSFORM, EORTC QLQ-C30 and FACT-Lym questionnaires were administrated at the time of randomization at baseline, day 29, day 64, day 126, month 6, and up to month 36.[18] In the SOC arm, PROs data were not collected after crossover to CAR T-cell therapy. Fewer than half the patients in each arm were included in the PRO population, and the PRO assessment completion rate from baseline to 6 months was greater than 45%. In terms of global health status/QOL and fatigue, the proportion of patients at 6 months reporting improved global health status/QOL was higher in the CAR T-cell arm vs the SOC arm (53% vs 14%), along with a higher incidence of reported worsened fatigue in the SOC arm vs the CAR T-cell arm (71% vs 18%). Thus, in both trials, PROs were significantly improved by multiple metrics in the CAR T-cell therapy vs SOC arms.

Clinical Summary and Future Perspectives

The initial inquiry regarding CAR T-cell therapy in the second-line setting in primary refractory and early relapsed disease has been generated by 3 soon-to-be landmark trials: ZUMA-7, BELINDA, and TRANSFORM. In this population, ZUMA-7 and TRANSFORM demonstrated a remarkably significant improvement in the primary endpoint of EFS in the CAR T-cell therapy over SOC arms, with a median EFS of 8.3 vs 2 months and 10.1 vs 2.3 months in ZUMA-7 and TRANSFORM, respectively, whereas BELINDA had an inferior EFS of only 3 months in both the CAR T-cell therapy and SOC arms. Similarly, ORRs were greater than 80% in ZUMA-7 and TRANSFORM, but only 38% in BELINDA. This disparity in treatment efficacy in rather congruently designed trials suggests that the tisa-cel product may be an outlier, and is consistent with previously reported lower response rates of tisa-cel compared with axi-cel and lisocabtagene maraleucel (liso-cel; Breyanzi, Juno/BMS) products.[8,19] A number of possibilities may account for this discrepancy. The time to peak CAR T-cell expansion with a 4-1BB costimulator is known to lag behind that with CD28, as illustrated by the reported peak CAR T-cell therapy levels at days 10 and 14 in BELINDA and TRANSFORM vs day 7 in ZUMA-7. Despite this, the ultimate impact of the costimulatory receptor is likely negligible given the high efficacy seen in both axi-cel (CD28) and liso-cel (4-1BB). The lower dose of lymphodepleting chemotherapy in BELINDA vs ZUMA-7 and TRANSFORM may also have an impact on cell expansion and persistence owing to lymphocytic fratricide and a crowding-out effect.[20,21] The initial assessment for an event in BELINDA and TRANSFORM occurred later (week 9/~day 71 and week 12/~day 84) compared with ZUMA-7 (week ~7/day 50), which, in theory, would account for a potential longer time to achieve response given slower CAR T-cell therapy expansion. Interestingly, the median target CAR dose is higher in BELINDA (2.9×10^8 cells) than in ZUMA-7 (1.4×10^8 cells in a typical 70-kg patient) or in TRANSFORM (1.0×10^8 cells). The time from randomization to infusion was longer in BELINDA, particularly for the non-US trial locations (median, 54 days), compared with ZUMA-7 (median, 29 days). This delay may provide an explanation regarding the high utilization of bridging therapy (83%) in BELINDA. It is unclear if the outcomes in the CAR T-cell therapy arm in BELINDA would have

Table 4. Outcomes, CAR T-Cell Therapy vs SOC

CAR T-Cell/SOC	ZUMA-7[12] **(n=180)**/(n=179)	BELINDA[13] **(n=162)**/(n=160)	TRANSFORM[14] **(n=92)**/(n=92)
Median EFS in mo (95% CI)	**8.3 (4.5-15.8)**/2 (1.6-2.8)	**3 (2.9-4.2)**/3 (2.9-4.2)	**10.1 (6.1-NR)**/2.3 (2.2-4.3)
PFS in mo (95% CI)	**14.7 (5.4-could not be estimated)**/3.7 (2.9-5.3)	**Not reported**	**14.8 (6.6-NR)**/5.7 (3.9-9.4)
HR for event, CAR T-cell therapy vs SOC (95% CI)	**0.5 (0.31-0.51)**	**0.95 (0.72-1.25)**	**0.35 (0.23-0.53)**
RR	**150 (83%)**/90 (50%)	**82 (50.6%)**/68 (43%)	**79 (86%)**/44 (48%)
Best ORR			
CR	**117 (65%)**/58 (32%)	**46 (28.4%)**/44 (28%)	**61 (66%)**/36 (39%)
PR	**33 (18%)**/32 (18%)	**29 (17.9%)**/24 (15%)	**18 (20%)**/8 (9%)
SD	**5 (3%)**/33 (18%)	**19 (11.7%)**/22 (14%)	**4 (4%)**/21 (23%)
PD	**21 (12%)**/38 (21%)	**50 (30.9%)**/46 (29%)	**6 (7%)**/24 (26%)
Unknown/Not evaluable	**4 (2%)**/18 (10%)	**18 (11.1%)**/24 (15%)	**3 (3%)**/3 (3%)
SOC crossover to CAR T-cell therapy	**100 (56%)**	**81 (51%)**	**47 (51%)**

CAR, chimeric antigen receptor; CR, complete response; EFS, event-free survival; HR, hazard ratio; mo, months; NR, not reached; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RR, response rate; DS, stable disease; SOC, standard of care.

improved with earlier infusion, but manufacturing time is certainly an important consideration for clinicians in selecting a CAR T-cell product, particularly for patients with aggressive and advanced disease, as it tends to be the case in the primary refractory and early-relapse setting. As seen in previous trials, axi-cel and liso-cel products had a near-zero rate of manufacturing failure. Interestingly, BELINDA did not report a manufacturing failure rate for tisa-cel. However, in the JULIET trial, 7% of enrolled patients had a tisa-cel manufacturing failure. Although we wish to avoid speculation, the concern must be raised—is it possible that manufacture failure/difficulty had an effect on the time of manufacture, or perhaps even on the efficacy of tisa-cel in the BELINDA trial? Lastly, BELINDA may have had a higher percentage of patients with higher-risk disease in terms of activated B-cell–like cell of origin by the Hans algorithm (32% in BELINDA vs 9% in ZUMA-7 and 23% in TRANSFORM), which may, in part, explain poorer outcomes.

Overall, the SOC arms in all 3 trials had better outcomes than historically reported for patients with primary refractory and early relapsed disease, although the SOC arms still had inferior EFS compared with CAR T-cell therapy in ZUMA-7 and TRANSFORM.[1] It is important to note that these improved outcomes in the SOC arms are at least in part due to approximately half of the patients in the SOC arms of all trials having crossover to CAR T-cell therapy. In ZUMA-7, a treatment switching sensitivity analysis was presented to account for the potential confounding impact of CAR T-cell therapy in the SOC arm, resulting in a HR of 0.58 that favored CAR T-cell therapy. This suggests that, in such high-risk patients, delaying CAR T-cell therapy may lead to worsened performance status secondary to complications of salvage/high-dose chemotherapy and auto-HSCT, and disease progression/evolution may result in inferior outcomes with delay of CAR T-cell therapy.

Nearly all patients in the CAR T-cell and SOC therapy arms in all trials reported an AE, and more than 80% experienced a grade 3 or higher AE. Cytopenias were common, but with mixed effects; neutropenia was nearly twice as common in the ZUMA-7 and TRANSFORM CAR T-cell arms than in the BELINDA CAR T-cell arm, but thrombocytopenia was higher in TRANSFORM than in BELINDA and ZUMA-7. The difference in the cell lines affected and the incidence of cytopenias is likely due to variability in laboratory draw time, differing doses of lymphodepleting chemotherapy (higher doses of fludarabine and cyclophosphamide in ZUMA-7 and TRANSFORM), and intrinsic differences in CAR T-cell function and the effect on tumor and marrow microenvironments. CRS and ICANS were more common in ZUMA-7 than in BELINDA and TRANSFORM, which is consistent with previously reported toxicities of each respective product. Interestingly, the incidence of ICANS in BELINDA and TRANSFORM was less than that

Table 5. CAR T-Cell Therapy Toxicities

	ZUMA-7[12] (n=180)	BELINDA[13] (n=162)	TRANSFORM[14] (n=92)
Adverse events			
Any grade	170 (100%)	160 (98.8%)	92 (100%)
Grade ≥3	155 (91%)	136 (84%)	85 (92%)
Cytopenias			
Neutropenia	121 (71%)	67 (41.4%)	75 (82%)
Leukopenia	55 (32%)	22 (31.6%)	14 (15%)
Thrombocytopenia	50 (29%)	59 (36.4%)	53 (58%)
Hypogammaglobulinemia	19 (11%)	Not reported	
CRS			
Any grade	157 (92%)	95 (61.3%)	45 (49%)
Grade ≥3	11 (6%)	8 (5.2%)	1 (1.1%)
ICANS			
Any grade	102 (60%)	16 (10.3%)	11 (12%)
Grade ≥3	36 (21%)	3 (1.9%)	4 (4%)
CAR T-cell–related death	1 (<1%)	4 (2.5%)	1 (1.1%)

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

reported in JULIET (10% vs 21%) and TRANSCEND (12% vs 35%), suggesting that increased toxicity is not seen when using CAR T-cell therapy earlier in the second-line setting. It is also possible that the decreased toxicity may be accounted for by early recognition and toxicity management in BELINDA and TRANSFORM (ZUMA-7 followed the same toxicity management of cohorts 1 and 2 in ZUMA-1).

Given the high incidence of AEs in all CAR T-cell therapy and SOC arms in these trials, PROs are of the utmost importance in truly assessing the effect of these therapies on patients, which can greatly assist in interpreting toxicities and can guide patient-physician dialogue on treatment modality discussions. Superior PROs in the CAR T-cell therapy arm at days 100 and 150 in ZUMA-7 and at day 100 in TRANSFORM suggest that, from a patient perspective, CAR T-cell therapy is better tolerated at these times. However, the findings were not significantly different at later times. Given that the patient numbers were small, these data must mature further prior to drawing any strong conclusions regarding PROs.

Finally, as noted in the presentation of ZUMA-7 at the 2021 ASH plenary session and applicable to clinical trials in general, the study populations were significantly skewed toward a White population. This is not representative of the incidence of LBCL across races and ethnicities, given that minorities in urban settings are often disproportionately affected. This skewing of the study population represents a weakness of all 3 trials, and of trials in general, despite efforts to increase minority participation in clinical trials.[22,23]

Conclusion

Now is an exciting time for CAR T-cell therapy as a new modality in the treatment of LBCL, particularly when conventional chemoimmunotherapy has failed. ZUMA-7 and TRANSFORM provide further evidence to suggest that using CAR T-cell therapy sooner in the second-line setting in the highest-risk patients may result in improved outcomes in terms of efficacy, survival, and PROs. The findings of the BELINDA trial did not support the use of CAR T-cell therapy in the second-line setting. Given congruent findings in only 2 of the 3 trials and the need for further long-term follow-up, a definitive conclusion is difficult to make. This is especially true when taking into consideration salient but different trial designs. However, in the most high-risk and chemorefractory patients, we believe there is a role for utilization of CAR T-cell therapy with both axi-cel and liso-cel to improve upon the historically poor outcomes in this setting, and our real-world practice and updated FDA labels reflect this.[24,25]

In our real-world clinical practice, the general approach to CAR T-cell therapy is to obtain liso-cel for older and frailer patients, patients with organ dysfunction, and patients who are otherwise at elevated risk for complications from CAR T-cell therapy. In those who require CAR T-cell therapy with the greatest expediency, we prefer

axi-cel. In young and fit patients, we offer the 2 therapies interchangeably. Furthermore, in our experience, patients who are eligible for CAR T-cell therapy in the second-line setting often present with rapidly proliferating disease and may require some form of bridging therapy (high-dose corticosteroids, chemoimmunotherapy, radiation therapy, or a combination of the three) in the time from leukapheresis to lymphodepleting chemotherapy.

Ultimately, long-term follow-up on large numbers of real-world patients will provide more guidance on which patients should receive second-line treatment with CAR T-cell therapy. Looking more broadly into the future, it remains to be seen if incorporating CAR T-cell therapy in early relapse and primary refractory indolent B-cell and mantle cell lymphoma may have advantages similar to those seen in ZUMA-7 and TRANSFORM for LBCL.

Disclosures

Dr Dahiya has served on the advisory boards of Kite, BMS, and Incyte; and has received research funding from Kite. The other coauthors have no disclosures to report.

Acknowledgments

We acknowledge the formatting and editing assistance of Kaylie Andersen, MS, in this manuscript.

References

1. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808.
2. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *J Clin Oncol*. 2014;32(31):3490-3496.
3. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28(27):4184-4190.
4. Philip T, Chauvin F, Bron D, et al. PARMA international protocol: pilot study on 50 patients and preliminary analysis of the ongoing randomized study (62 patients). *Ann Oncol*. 1991;2(suppl 1):57-64.
5. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995;333(23):1540-1545.
6. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone Marrow Transplant*. 2016;51(1):51-57.
7. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-Cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544.
8. Schuster SJ, Bishop MR, Tam CS, et al; JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380(1):45-56.
9. Chong EA, Ruella M, Schuster SJ; Lymphoma Program Investigators at the University of Pennsylvania. Five-year outcomes for refractory B-cell lymphomas with CAR T-cell therapy. *N Engl J Med*. 2021;384(7):673-674.
10. Jacobson CA, Locke FL, Ghobadi A, et al. Long-term (5 year) overall survival in Zuma-1, the pivotal study of axicabtagene ciloleucel in patients with refractory large B-cell lymphoma [ASTCT and CIBMTR abstract 10]. *Transplant Cell Ther*. 2022;28(3)(suppl).
11. Shadman M, Pasquini MC, Ahn KW, et al. Autologous transplant vs chimeric antigen receptor T-cell therapy for relapsed DLBCL in partial remission. *Blood*. 2021;139(9):1330-1339.
12. Locke FL, Miklos DB, Jacobson CA, et al; all ZUMA-7 Investigators and Contributing Kite Members. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. *N Engl J Med*. 2022;386(7):640-654.
13. Bishop MR, Dickinson M, Purtill D, et al. Second-line tisagenlecleucel or standard care in aggressive B-cell lymphoma. *N Engl J Med*. 2022;386(7):629-639.
14. Kamdar M, Solomon SR, Arnason J, et al; TRANSFORM Investigators. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. *Lancet*. 2022;399(10343):2294-2308.
15. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.
16. Hlubocky FJ, Webster K, Cashy J, Beaumont J, Cella D. The development and validation of a measure of health-related quality of life for non-Hodgkin's lymphoma: the Functional Assessment of Cancer Therapy—Lymphoma (FACT-Lym). *Lymphoma*. 2013;147176. https://doi.org/10.1155/2013/147176.
17. Elsawy M, Chavez JC, Avivi I, et al. Patient-reported outcomes in ZUMA-7, a phase 3 study of axicabtagene ciloleucel in second-line large B-cell lymphoma. *Blood*. 2022;140(21):2248-2260.
18. Abramson JS, Solomon SR, Arnason J, et al. Improved quality of life (QOL) with lisocabtagene maraleucel (liso-cel), a CD19-directed chimeric antigen receptor (CAR) T cell therapy, compared with standard of care (SOC) as second-line (2L) treatment in patients (pts) with relapsed or refractory (R/R) [ASH abstract 3845]. *Blood*. 2021;138(1)(suppl).
19. Jain MD, Bachmeier CA, Phuoc VH, Chavez JC. Axicabtagene ciloleucel (KTE-C19), an anti-CD19 CAR T therapy for the treatment of relapsed/refractory aggressive B-cell non-Hodgkin's lymphoma. *Ther Clin Risk Manag*. 2018;14:1007-1017.
20. Bechman N, Maher J. Lymphodepletion strategies to potentiate adoptive T-cell immunotherapy - what are we doing; where are we going? *Expert Opin Biol Ther*. 2021;21(5):627-637.
21. Fabrizio VA, Boelens JJ, Mauguen A, et al. Optimal fludarabine lymphodepletion is associated with improved outcomes following CAR T-cell Therapy. *Blood Adv*. 2021.
22. Blansky D, Mantzaris I, Rohan T, Hosgood HD III. Influence of rurality, race, and ethnicity on non-Hodgkin lymphoma incidence. *Clin Lymphoma Myeloma Leuk*. 2020;20(10):668-676.e5.
23. Wallington SF, Dash C, Sheppard VB, et al. Enrolling minority and underserved populations in cancer clinical research. *Am J Prev Med*. 2016;50(1):111-117.
24. FDA approves lisocabtagene maraleucel for second-line treatment of large B-cell lymphoma [press release]. ESMO. https://www.esmo.org/oncology-news/fda-approves-lisocabtagene-maraleucel-for-second-line-treatment-of-large-b-cell-lymphoma. July 12, 2022. Accessed February 14, 2023.
25. FDA approves axicabtagene ciloleucel for second-line treatment of large B-cell lymphoma [press release]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-axicabtagene-ciloleucel-second-line-treatment-large-b-cell-lymphoma. April 1, 2022. Accessed February 14, 2023.