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Review

The role of CAR-T cell therapy as second line in diffuse large B-cell lymphoma

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***Abstract*:** For approximately three decades, autologous hematopoietic cell transplantation (auto-HCT) has been the standard of care for patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after frontline therapy. This approach is limited due to the intensity of chemotherapy and the proportion of patients who relapse after auto-HCT. Since the approval of anti-CD19 chimeric antigen receptor T-cell (CAR-T) therapy and novel agents, the treatment paradigm for DLBCL has changed remarkably. Anti-CD19 CAR-T therapy was first approved for relapsed DLBCL after two or more previous lines of therapy with long-lasting responses, with over 50% of patients still alive at 5-year follow-up. Here, we discuss recent randomized phase 3 clinical trials using axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel in the second-line therapy setting compared with the standard of care in transplant-eligible patients who have DLBCL R/R within 12 months of completing chemo-immunotherapy, potentially changing the treatment algorithm for DLBCL.

Keywords: CAR T cell therapy, early relapse DLBCL, primary refractory DLBCL, Second line DLBCL

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), with an estimated annual incidence rate of 5.3 out of 100,000 in the United States and a reported crude annual incidence of 3.8 out of 100,000 in Europe.[1,2] The addition of rituximab to the chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has led to improved outcomes in DLBCL. However, about one-third of patients still relapse or become refractory to this regimen.[3–5] The PARMA trial established the role of second-line autologous hematopoietic cell transplantation (auto-HCT) for chemotherapy-sensitive patients following dexamethasone, cisplatin, and cytarabine (DHAP) in the pre-rituximab era.[6] Subsequently, the CORAL and NCIC CTG LY12 studies compared different options for salvage chemotherapy prior to auto-HCT. The CORAL study compared rituximab, ifosfamide, etoposide, and carboplatin (R-ICE) to rituximab-DHAP (R-DHAP) followed by auto-HCT for patients with chemotherapy-responsive disease. The NCIC CTG LY12 study compared rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP) to R-DHAP, and the results for both studies showed no substantial difference between such salvage chemotherapy options. However, both trials showed that patients with refractory disease or those who relapse within 12 months of completing chemo-immunotherapy had worse outcomes.[7,8]

What is the outcome after auto-HCT relapse?

In the second-line setting, the objective response to salvage therapy is between 40% and 60%, and the 2- to 3-year event-free survival (EFS) is between 35% and 50%.[7–9] Despite its efficacy, many patients will not respond to second-line therapy and will relapse after auto-HCT or will not be eligible for auto-HCT. This shows the poor prognosis of relapse DLBCL prior to the era of anti-CD19 chimeric antigen receptor T cell (CAR-T) therapy (Figure 1).[10] Epperla *et al.*[11] analyzed the outcomes of patients with relapsed disease post–auto-HCT and found that the

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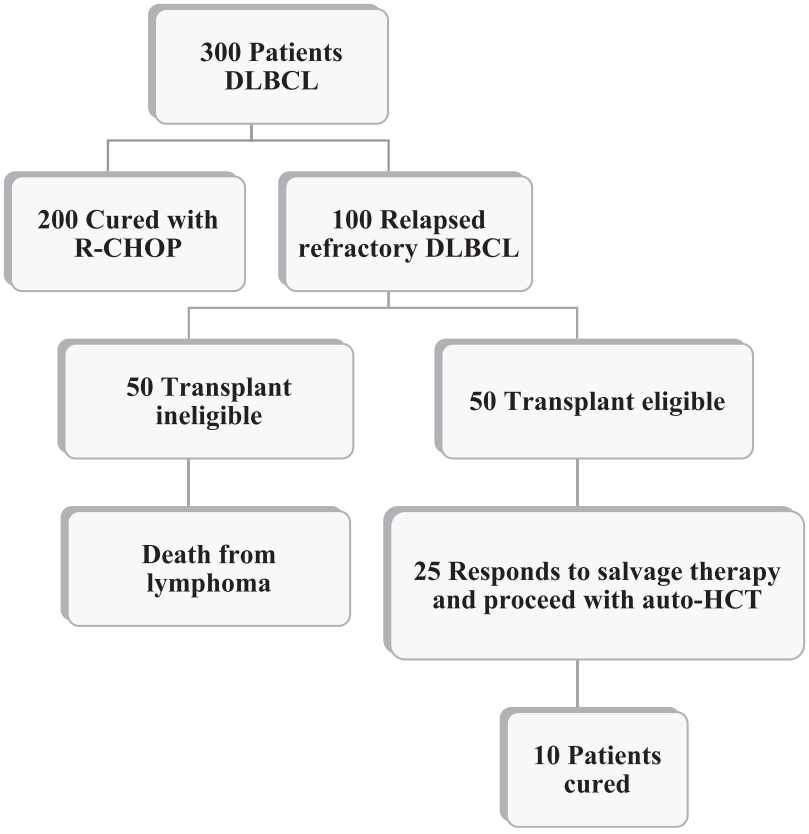

Figure 1. Limited benefit of auto-HCT in patients with R/R DLBCL (prior anti-CD19 CART).[9]
Auto-HCT indicates autologous hematopoietic stem cell transplant.
Figure presented with permission: Hematology Am Soc Hematol Educ Program (2011) 2011 (1): 498–505.
DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed/refractory.

post-relapse median overall survival (OS) was 9.8 months. Furthermore, when the assessment was based on the response status prior to auto-HCT, patients who experienced a partial response (PR) had a worse outcome than those in complete response (CR), as the median post auto-HCT relapse OS was 7.1 *versus* 17.8 months, respectively.[11] The SCHOLAR-1 study confirmed the poor outcome for patients with refractory DLBCL (defined as progressive disease being the best response to any line of chemotherapy, stable disease as the best response to ⩾4 cycles of first-line therapy, more than two regimens of later-line therapy, or relapse within 12 months). The SCHOLAR-1 study was an observational cohort study that evaluated the outcome for patients who had refractory DLBCL from four sources (MD Anderson Cancer Center, Molecular Epidemiology Resource of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence, the NCIC CTG LY12 study, and the CORAL study) included 636 patients. It showed that the response rate to subsequent therapy was 26% (20–31%) with a CR rate of 7% (2–15%), and the response rate for primary refractory was 20% with a CR rate of 3%. The outcomes were inferior, with a median OS of 6.3 months. For patients who had an auto-HCT, the median OS was 8.7 months.[12]

Anti-CD19 CAR-T cell therapy for LBCL in third-line setting

Anti-CD19 CAR-T therapy made a considerable shift in the treatment landscape for patients with NHL.[13–17] Axicabtagene ciloleucel (axi-cel) was first approved by the US Food and Drug Administration (FDA) on 18 October 2017, for patients with relapsed LBCL after two or more lines of therapy. This was followed by FDA

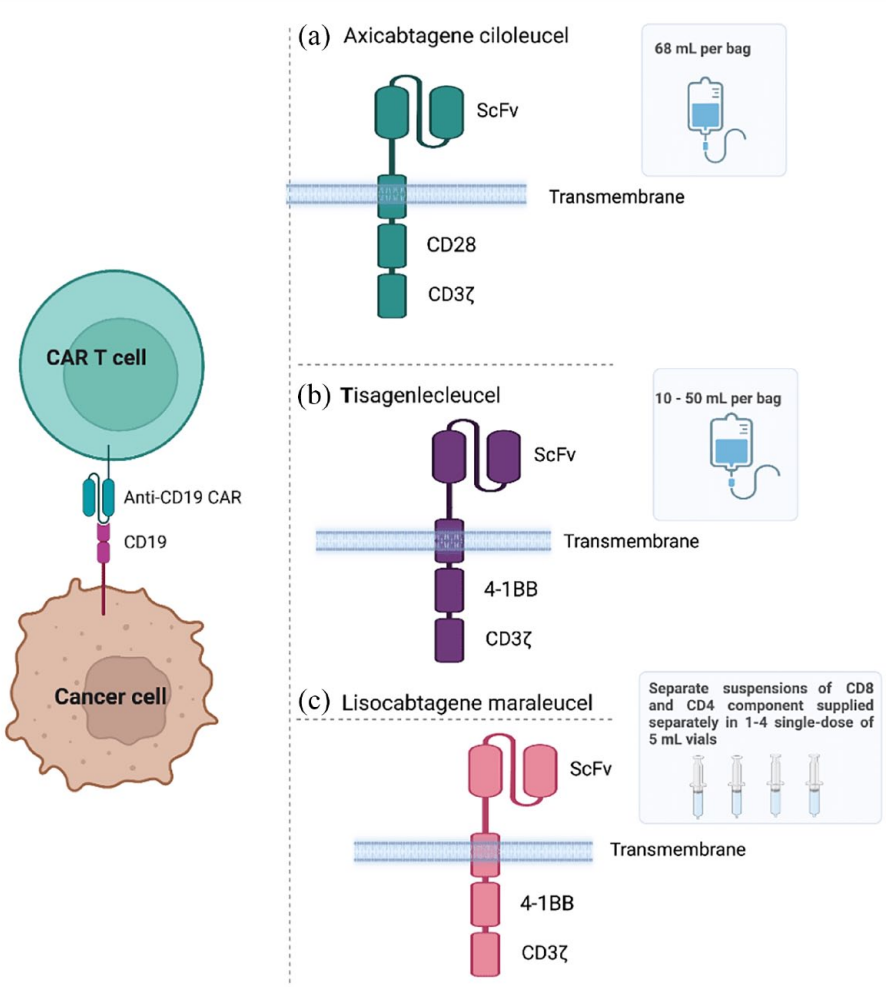

Figure 2. Chimeric antigen receptor T-cell structure.
CAR-T indicates chimeric antigen receptor T-cell.

approval of tisagenlecleucel (tisa-cel) on 1 May 2018, and lisocabtagene maraleucel (liso-cel) on 5 February 2021. The three products differ in the co-stimulatory domain, viral vector used, incidence of cytokine release syndrome (CRS), incidence of immune effector cell-associated neurotoxicity syndrome (ICANS), and the trial design that led to each FDA approval (Figure 2).

Axi-cel is an autologous anti-CD19 CAR-T product with a CD28 intracellular co-stimulatory domain transduced with a retroviral vector. FDA approval was based on the pivotal ZUMA-1 trial in which 111 patients enrolled with relapsed or refractory (R/R) LBCL (21% had relapsed disease after transplant, 77% had disease resistance to second line, 26% had primary refractory disease, and 69% received three or more prior lines of therapy). In ZUMA-1, no bridging chemotherapy was allowed, and 101 patients received 2×10^6CAR cells/kg with fludarabine (Flu) 30 mg/m^2 and cyclophosphamide (Cy) 500 mg/m^2 for lymphodepletion. The primary analysis at a median follow-up of 15.4 months showed an overall response rate (ORR) and CR of 82% and 54%, respectively. After a median follow-up of 27.1 months, the median duration of response and progression free survival (PFS) were 11.1 and 5.9 months, respectively. The 5-year OS reported most recently was 42.6%.[18] Therapy was associated with potential toxicities such as CRS and ICANS. CRS of all grades and grade >3

occurred in 93% and 13% of patients, respectively. ICANS of all grades and grade >3 occurred in 64% and 28% of patients, respectively.[13,19] Real-world data from the US Lymphoma CAR-T Consortium confirmed the safety and efficacy of axi-cel to be comparable with ZUMA-1, with an ORR of 82% and median PFS of 8.3 months, even though 43% of patients included would not have met the eligibility for ZUMA-1.[20]

Tisa-cel was approved based on the JULIET trial for R/R LBCL. Tisa-cel contains 4-1BB as an intracellular domain and is transduced with a lentivirus. In this trial, 165 patients enrolled, and 111 received their cell infusions with a viable anti-CD19 CAR-T cell dose of 0.1×10^8 to 6×10^8 (49% had relapsed disease after transplant and 61% had refractory disease). The conditioning regimens consisted in Flu at 25 mg/m^2 and Cy at 250 mg/m^2 for 3 days (73%) or bendamustine at 90 mg/m^2 for 2 days (20%) with eight patients (7%) who did not receive lymphodepletion. Bridging therapy was allowed and given to 92% of patients. In the evaluable patients, the ORR and CR rates were 52% and 40%, respectively. The responses were durable, especially for those achieving CR. The long-term follow-up for the JULIET trial had a median follow-up of 40.3 months, reported a median PFS of 2.9 months, and had a median OS of 11.1 months. CRS and ICANS were reported at 58% (grade >3, 22%) and 21% (grade >3, 12%), respectively.[14,21]

The FDA approved liso-cel based on the TRANSCEND trial, which contains 4-1BB as an intracellular domain and transduced with a lentivirus. This trial also allowed bridging therapy (given to 59% of enrolled patients). The study included 256 patients, and the lymphodepletion regimen used was Flu at 30 mg/m^2 and Cy at 300 mg/m^2. Patients included in the efficacy analysis received infusions (1:1 ratio of CD4: CD8 at three different dose levels, 50×10^6, 100×10^6, and 150×10^6 anti-CD19 CAR-T cells). The objective response was 73% (53% had CR), the median PFS was 6.8 months, and the median OS was 21.1 months. Any grade CRS occurred in 42% of patients, and grade >3 CRS occurred in 2% of patients, with a median time from infusion to CRS onset of 5 days. Any grade ICANS occurred in 30% of patients, and grade >3 ICANS occurred in 10% of patients, with a median time from infusion to ICANS onset of 9 days.[15] Most recently, 2-year follow-up data were presented, which showed the probability of continued response (49.5%), continued PFS (40.6%), and continued OS (50.5%).[22]

Second-line anti-CD19 CAR-T cell therapy

After the approval of axi-cel, tisa-cel, and liso-cel for R/R LBCL in the third line, and with the favorable outcomes compared with large historical studies such as CORAL, NCIC CTG LY12, and SCHOLAR-1,[7,8,12,23] the next logical step was to challenge the paradigm of salvage chemotherapy followed by auto-HCT in the second-line.

The ZUMA-7, BELINDA, and TRANSFORM are all international, multicenter phase 3 randomized clinical trials comparing anti-CD19 CAR-T cell therapy as the second-line to salvage chemotherapy followed by auto-HCT in patients with R/R LBLC. This was defined as refractory to first-line therapy or relapse within 12 months after completing the first line of chemo-immunotherapy. In the following section, we will discuss in detail the results of the three randomized trials.[24–26]

Study design, eligibility, and end-point definition

The ZUMA-7 trial enrolled patients who were 18 years or older (no upper age limit) and then randomized patients prior to leukapheresis into a 1:1 ratio to receive axi-cel or standard of care (SOC) with two or three cycles of pre-specified selection of platinum-based chemotherapy (rituximab etoposide, methylprednisolone, cisplatin, and cytarabine [R-ESHAP], R-DHAP, R-ICE, and R-GDP) followed by auto-HCT if PR/CR was achieved. Unlike the BELINDA or TRANSFORM trials, ZUMA-7 did not allow bridging chemotherapy, but steroids could be used. In addition, crossover was not allowed, as opposed to the other trials. The lymphodepletion regimen was consistent with the current label of axi-cel Flu (30 mg/m^2) and Cy (500 mg/m^2) for 3 days, followed by 2×10^6 anti CD19 CAR-T/kg. The primary end point was EFS, defined as the time from randomization to the earliest date of disease progression, the start of a new lymphoma therapy, death from any cause, or best response of stable disease up to 150 days (21.4 weeks).

The BELINDA trial enrolled patients who were 18 years or older (no upper age limit). All enrolled patients underwent leukapheresis, followed by randomization into a 1:1 ratio to receive tisa-cel or SOC; thus, patients in both arms underwent leukapheresis for potential tisa-cel manufacturing, as the trial allowed crossover after confirming stable disease or progression of disease at >12-week assessment. Bridging chemotherapy was allowed from pre-specified regimens (R-ICE, R-GDP, R-DHAP, and R-GemOx), and it allowed more than one cycle for patients who achieved inadequate response at the 6-week positron emission tomography (PET). Similar to the JULIET trial, the lymphodepletion used was FluCy or bendamustine, followed by a single infusion of 0.6 to 6×10^8 anti-CD19 CAR viable T cells. Patients randomized to SOC received one of four pre-specified chemotherapy regimens (same as bridging) followed by auto-HCT for those who achieved PR/CR. Patients who achieved inadequate response at the 6-week PET could receive a second chemotherapy regimen. The primary end point was EFS, defined as the time from randomization to stable disease or progressive disease at >12-week-assessment or death at any time (disease progression requiring a second cycle or another line of bridging chemotherapy was not considered an event if it occurred before week 12 assessment).

The TRANSFORM trial enrolled patients 18–75 years old; randomizing patients into a 1:1 ratio to receive liso-cel or SOC occurred after leukapheresis. SOC received three cycles of chemoimmunotherapy from a pre-specified selection (R-DHAP, R-ICE, R-GDP) followed by auto-HCT. The trial allowed patients with secondary central nervous system (CNS) lymphoma. Crossover was allowed if there was a failure to respond to SOC by week 9, disease progression at any time, or the start of any new therapy after auto-HCT. Unlike BELINDA, the TRANSFORM trial allowed only one cycle of bridging therapy, with similar regimens as used in the SOC arm. The lymphodepletion regimen used was FluCy at the doses per liso-cel label, followed by a target dose of 100×10^6 anti-CD19 CAR-T cells (1:1 ratio of CD4: CD8). The primary end point was EFS, defined as the time from randomization to death from any cause, progressive disease, or failure to achieve CR or PR by 9 weeks after randomization or the start of new antineoplastic therapy. Product, trial design, demographics are summarized in Table 1.

Results

Axi-cel versus *SOC*

In the ZUMA-7 trial, 437 patients were screened, 359 patients were randomized, 180 were assigned to axi-cel, and 179 were assigned to SOC. Baseline characteristics were well balanced; the median age was 59 years (range, 21–81), 74% of patients had primary refractory disease, 45% had a high second-line age-adjusted international prognostic index (sAAIPI), 79% had stage III–IV, and 16% of patients had high-grade lymphoma including double hit lymphoma (DHL) and triple hit lymphoma (THL). Among patients in the axi-cel arm, 178 (99%) underwent leukapheresis, 170 (94%) received axi-cel, and 65 (36%) received steroids as bridging therapy. Compared with BELINDA and TRANSFORM trials, in Zuma-7, the axi-cel arm had a shorter median time from leukapheresis to product release (13 days) and median time to cell infusion (29 days). In the SOC arm, 64 of 80 patients who achieved response (PR/CR) underwent auto-HCT. At a median follow-up time of 24.9 months, the ZUMA-7 trial met its primary end point with a median EFS of 8.3 months (95% confidence interval [CI], 4.5–15.8) for axi-cel *versus* 2 months (95% CI, 1.6–2.8) for SOC with a hazard ratio (HR) of 0.40 (95% CI, 0.31–0.51; $p<0.001$). The ORR and CR rates were significantly higher with axi-cel compared with the SOC arm (Table). Median PFS was 14.7 months *versus* 3.7 months (HR, 0.49), and the 24-month PFS was 46% *versus* 27% for axi-cel and SOC, respectively. Out of 144 patients who progressed in the SOC arm, 56% received subsequent cellular immunotherapy off protocol. Although not statistically significant, axi-cel showed a trend toward an improvement in OS, with a median OS not reached (NR) *versus* 35.1 months for axi-cel and SOC, respectively (HR, 0.73; 95% CI, 0.53–1.01; $p=0.054$), and 2-year OS was 61% for axi-cel *versus* 52% for SOC, with longer follow-up time needed.

Tisa-cel versus *SOC*

In the BELINDA trial, 396 patients were screened, and 322 underwent leukapheresis, with

Table 1. Product, trial design, demographics, results, and toxicity.

	ZUMA-7 ($n=359$)		BELINDA ($n=322$)		TRANSFORM ($n=184$)	
Product						
	Axicabtagene ciloleucel		Tisagenlecleucel		Lisocabtagene maraleucel	
CAR-T cell dose	2×10^6 anti CD19 CAR-T/kg		0.6 to 6×10^8 CAR viable T cells		100×10^6 CAR-T cells (1:1 ratio of CD4:CD8)	
Co-stimulatory domain	CD28/CD3 zeta		4-1BB/CD3 zeta		4-1BB/CD3 zeta	
Viral victor	Retrovirus		Lentivirus		Lentivirus	
Lymphodepletion	Flu 30 mg/m^2 and Cy 500 mg/m^2 for 3 days		Flu 25 mg/m^2 and Cy 250 mg/m^2 for 3 days or bendamustine 90 mg/m^2 for 2 days		Flu 30 mg/m^2 and Cy 300 mg/m^2 for 3 days	
Trial design						
Inclusion criteria	Primary refractory or relapsed ⩽12 months, EF ⩾50%, CrCL ⩾60 mL/min		Primary refractory or relapsed ⩽12 months, EF ⩾45%, serum Cr ⩽1.5, or eGFR ⩾60 mL/min		Primary refractory or relapsed ⩽12 months, EF ⩾40%, CrCL ⩾45 mL/min	
Histology	DLBCL-NOS, transformed FL, HGBCL with MYC rearrangement with BCL2/6, HGBCL without MYC rearrangement, EBV positive DLBCL, and leg type cutaneous DLBCL		DLBCL-NOS, transformed indolent lymphoma, HGBCL with MYC rearrangement with BCL2/6, HGBCL without MYC rearrangement, FL grade 3B, PMBCL, T/H-RLBCL, and intravascular LBCL		DLBCL-NOS, transformed indolent NHL lymphoma, HGBCL with MYC and BCL2/6, T/H-RLBCL, FL grade 3B, and PMBCL	
Age, years	⩾18		⩾18		18–75	
Response assessment time	150 days (21.4 weeks)		12 weeks		9 weeks	
EFS definition (time from randomization)	PD, start new therapy, Death, best response of stable disease up to 150 days		SD or PD at ⩾12 weeks or death at any time		PD or failure to achieve CR/PR ⩾9 weeks, start of new therapy, or death at any time	
Time of leukapheresis	After randomization		Before randomization		Before randomization	
Allowed crossover	No		Yes		Yes	
Bridging therapy allowed	20–40 mg of dexamethasone or equivalent		R-ICE, R-GDP, R-DHAP, R-GemOX		R-ICE, R-GDP, R-DHAP	
Demographics						
	Axi-cel	SOC	Tisa-cel	SOC	Liso-cel	SOC
No.	180	179	162	160	92	92
Male (%)	110 (61)	127 (71)	103 (63)	98 (61)	44 (48%)	61 (66%)
Median age, years (range)	58 (21–80)	60 (26–81)	59.5 (19–79)	58 (19–77)	60 (20–74)	58 (26–75)
Age ⩾65, %	28	32	33	28.8	39	27

(Continued)

Table 1. (Continued)

	ZUMA-7 (*n* = 359)		BELINDA (*n* = 322)		TRANSFORM (*n* = 184)	
sAAIPI ⩾2 or IPI ⩾2 (%)	82 (46)	79 (44)	106 (65.4)	92 (57.5)	36 (39)	37(40)
Germinal center B-cell (%)	109 (61)	99 (55)	46 (28.4)	63 (39.4)	45 (49)	40 (43)
Activated B-cell (%)	16 (9)	9 (5)	52 (32.1)	42 (26.2)	21 (23)	29 (32)
Primary refractory (%)	133 (74)	131 (73)	107 (66)	107 (67)	67(73)	68(74)
HGBCL (%)	31 (17)	26 (15)	39 (24.1)	27 (17)	22 (24)	21 (23)
Elevated LDH (%)	101 (56)[a]	94 (53)[a]	NR	NR	10 (11)[b]	10 (11)[b]
Median SPD cm^2	21.2	20.7	NR	NR	11.4	15.7
Stage III-IV (%)	139 (77)	146 (82)	107 (66)	98 (61.2)	68 (74)	63 (68)
Bridging corticosteroid (%)	65 (36)	–	–	–	–	–
Bridging chemotherapy (%)	–	–	135 (83.3)	–	58 (63)	–
Cycles of bridging chemotherapy allowed	0		No limit	–	1	–
Manufacturing failure, %	NR	–	3	–	1	–
Received CAR-*T* (%)	170 (94)	–	155 (95.7)	–	89 (97.8)	–
Received auto-HCT (%)	–	65 (36)	–	52 (32.5)	–	43 (46.5)
Per protocol crossover (%)	–	–	–	81 (50.6)	–	50 (54.3)
Off protocol crossover (%)	–	100 (56)	–	–	–	–
Median time from leukapheresis to CAR-T infusion (days)	29	–	52	–	36	–
Result						
Median follow-up time, months	24.9		10		6.2	
Median EFS, months	8.3	2	3	3	10.1	2.3
EFS, %[c]	41% at 24 months	16% at 24 months	NR	NR	63% at 6 months	33% at 6 months
ORR, %	83	50	46.3	42.5	86	48
CR, %	65	32	28.4	27.5	66	39
Median PFS, months	14.7	3.7	NR	NR	14.8	5.7
PFS rate	46% at 24 months	27% at 24 months	–	–	44.5% at 12 months	23.7 at 12 months
Median OS, months[d]	Not reached	25.7	16.9	15.3	Not reached	16.4

(Continued)

Table 1. (Continued)

	ZUMA-7 (*n* = 359)		BELINDA (*n* = 322)		TRANSFORM (*n* = 184)	
Toxicity						
CRS any grade, %	92	–	61.3	–	49	–
CRS grade ⩾3, %	6	–	5.2	–	1	–
Median time to CRS onset, days	3	–	4	–	5	–
ICANS any grade, %	60	20	10.3	–	12	–
ICANS grade ⩾3, %	21	1	1.9	–	4	–
Median time to ICANS onset, d	7	–	5	–	11	
Tocilizumab use, %	65	–	53.2	–	24	–
Dexamethasone use, %	32		14.7	–	17	–

AAIPI, age-adjusted international prognostic index; BCL2/6, B-cell lymphoma protein 2 and/or 6; CAR-T, chimeric antigen receptor T-cell; CR, complete response; CRS, cytokine release syndrome; Cy, cyclophosphamide; DLBCL-NOS, diffuse large B cell lymphoma, not otherwise specified; EFS, event-free survival; FL, follicular lymphoma; Flu, fludarabine; HGBCL, high-grade B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NHL, non-Hodgkin lymphoma; NR, not reported; ORR, overall response rate; OS, overall survival; PD, progression disease; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphoma; R-DHAP, rituximab, dexamethasone, cisplatin and cytarabine; R-GDP, rituximab, gemcitabine, dexamethasone, and cisplatin; R-GemOX, rituximab, gemcitabine, oxaliplatin; R-ICE, rituximab, ifosfamide, etoposide and carboplatin; SD, table disease; SPD, sum of the product of perpendicular diameters; T/H-RLBCL, T-cell/histiocyte-rich large B-cell lymphoma.
[a]Elevated LDH defined as above the upper limit of the normal range.
[b]LDH ⩾500 units/L.
[c]For the ZUMA-7 trial, EFS reported for 24 months and for the BELINDA trial, EFS reported for 6 months.
[d]Not significant.

162 patients randomized to tisa-cel and 160 patients randomized to SOC. The median age was 59 years (range, 19–79), with primary refractory disease in 66.5% and relapse in less than 6 months in 19.3%. The tisa-cel arm had more patients with high-grade B-cell lymphoma (24.1% *versus* 16.9%) and international prognostic index (IPI) >2 (65.4% *versus* 57.5%). Bridging chemotherapy was administered to 135 patients (83.3%), 58 (35.8%) patients received one cycle, and 77 (47.5%) patients received at least two cycles. Longer time needed for cell manufacturing was documented as the median time from leukapheresis to manufacturing, and shipping was 23.5 days to US sites and 28 days to non-US locations, whereas the median time from leukapheresis to tisa-cel infusion was 52 days (41 days in the United States and 57 days in non-US locations). The median time from randomization to auto-HCT was 3 months. Among 162 assigned to tisa-cel, 155 (95.7%) received tisa-cel, and among 160 patients assigned to SOC, 52 out of 68 patients who achieved response (PR/CR) received auto-HCT. Eighty-one (50.6%) patients who progressed in the SOC arm crossed over to receive tisa-cel; 71 of them did not receive auto-HCT (median time from randomization to crossover, 4.3 months). By the time of data cutoff and with a median follow-up time of 10 months, the BELINDA trial failed to meet its primary end point, as EFS did not differ significantly, with a median EFS of 3 months in both groups (HR, 1.07; 95% CI, 0.82–1.4; $p = 0.61$). Response at week 6 (considered the last assessment before tisa-cel infusion) occurred in 38.3% of patients who received tisa-cel and 53.8% of patients who received SOC, and progression of disease was noted in 25.9% in tisa-cel and 13.8% in SOC, respectively. OS data were immature at the time of this review.

Liso-cel versus *SOC*

In the TRANSFORM trial, a total of 184 patients underwent leukapheresis with 92 randomized to the liso-cel arm and 92 to the SOC arm. The

median age was 60 years (range, 20–75), with primary refractory disease in 73.3%, relapse in ⩽12 months in 26.6%, and sAAIPI >2 in 39.6%. Only one cycle of bridging therapy was allowed, and 58 patients (63%) received bridging therapy. The median time from leukapheresis to product availability was 26 days, and the median time from leukapheresis to cell infusion was 36 days. Moreover, in the SOC, 43 of 44 patients who achieved response (PR/CR) were able to proceed to auto-HCT. A total of 50 patients crossed over to the liso-cel arm. After a median follow-up of 6.2 months, the TRANSFORM trial met its primary end point, with a median EFS of 10.1 months for liso-cel and 2.3 months for SOC (HR, 0.35) and a 65% risk reduction ($p < 0.001$). Furthermore, 66% and 39% of patients achieved CR in the liso-cel and the SOC arm, respectively. The median PFS was 14.8 months and 5.7 months for liso-cel and SOC, respectively (HR, 0.41), with a 59% risk reduction. The OS was immature at the time of analysis, with a median OS not reached (15.8, not reached) for liso-cel *versus* 16.4 months (11, not reached) for SOC.

Toxicity

Cross-trial comparisons should be approached with caution. Toxicity profiles in the second-line were similar to those previously reported in pivotal trials in the third line.[13–15]

Any toxicities of grade ⩾3 occurred in 91%, 84%, and 85% in axi-cel, tisa-cel, and liso-cel, respectively. In the ZUMA-7 trial, all patients had at least one reported adverse event. More CRS and ICANS were reported in ZUMA-7 than the other two trials, and any grade CRS occurred in 92% of patients and grade >3 in 6% of patients. The median time to onset of CRS was 3 days after the infusion, and the median duration was 7 days. Tocilizumab was administered to 65%, glucocorticoids to 24%, and vasopressors to 6% of patients. ICANS occurred in 60% of patients in the axi-cel group *versus* 20% of patients in the SOC group, and grade ⩾3 toxicities occurred in 21% of patients in the axi-cel arm and 1% of patients in the SOC arm, with corticosteroids used in 32%. The median time to onset of ICANS was 7 days and 23 days, and the median duration was 9 days and 23 days in axi-cel and SOC, respectively. Prolonged cytopenia of grade ⩾3 (present beyond day 30) was higher in the axi-cel arm than the SOC arm (29% *versus* 19%). Similarly, hypogammaglobulinemia (11% *versus* 1%) and grade ⩾3 infections were higher in axi-cel than SOC (11% *versus* 1% and 14% *versus* 11%, respectively).

In the BELINDA trial, 98.8% of patients had at least one adverse event. Any grade CRS occurred in 61.3%, and grade ⩾3 CRS occurred in 5.2%, with a median time from infusion to CRS of 4 days and time to resolution of 5 days. Tocilizumab was given to 53.2% of patients, and corticosteroids were given to 14.7% of patients that received tisa-cel initially or after crossover. Any grade ICANS occurred in 10.3%, and grade ⩾3 occurred in 1.9%. The median time from infusion to ICANS onset was 5 days, and the time to resolution was 9 days. Data for prolonged cytopenia were not reported at the time of this review.

In the TRANSFORM trial, 98.8% had at least one adverse event. Any grade CRS occurred in 49%, and only one patient had grade 3 CRS (1%) on day 9 that resolved in 2 days. The median time to onset of CRS was 5 days, and the median time to resolution was 4 days. Furthermore, 24% of patients received tocilizumab and 17% received corticosteroids. Any grade ICANS occurred in 12.4%, and 4% of patients had grade ⩾3. The median time from infusion to ICANS onset was 11 days, and the time to resolution was 6 days. Prolonged cytopenias (beyond day 35) were higher in liso-cel (43%) than SOC (3%), but grade ⩾3 infections occurred more in the SOC arm (21%) compared with the liso-cel arm (15%). Longer follow-up is needed regarding long-term toxicity. Results are summarized in Table 1.

Discussion

Unlike the BELINDA trial, ZUMA-7 and TRANSFORM met their primary end point of EFS, and the results can be practice for patients with early relapse or refractory LBLC. As of 1 April 2022, the FDA approved axi-cel for adult patients with LBCL that is refractory to first-line chemo-immunotherapy or relapsed within 12 months of first-line chemo-immunotherapy; this was followed by the approval of liso-cel on 24 June 2022, for patients with LBCL with primary refractory or early relapse within 12 months of frontline treatment or in transplant-ineligible patients.[24,26,27]

In addition, the PFS was also superior in the ZUMA-7 and TRANSFORM trials, and both showed a trend toward an improvement in OS and will need a longer follow-up to show a potential difference.

Although cross-trial comparisons should not be performed, all three trials had the same indication of second-line anti-CD19 CAR-T in patients with refractory or relapse within 12 months from completing the first line of chemo-immunotherapy by exploring EFS as their primary end point. However, some differences may have impacted the difference in the results seen.

The median age was similar across all three trials (58–60 years). The number of female participants in the CAR-T arm were lower in the BELINDA and ZUMA-7 trials (37% and 39%), while in TRANSFORM, it was 52%. Comparing the tumor burden across all three trials is challenging, as it was reported in a heterogeneous fashion. For instance, the median sum of the product of perpendicular diameters and lactate dehydrogenase were reported only in ZUMA-7 and TRANSFORM, and they were similar in both arms. ZUMA-7 and TRANSFORM reported sAAIPI $\geqslant$2; however, the BELINDA trial reported an IPI score of $\geqslant$2.

In addition, more patients in the BELINDA trial had activated B-cell–like subtype (ABC) compared with ZUMA-7 and TRANSFORM. ABC has been reported to be associated with a worse outcome than the germinal center subtype in the frontline setting.[28] Another marked difference is bridging chemotherapy. In ZUMA-7, bridging chemotherapy was not allowed, TRANSFORM only allowed one cycle of bridging chemotherapy (63% received one cycle), and the BELINDA trial did not limit the number of bridging chemotherapy cycles; thus, patients received as many as the investigator felt to be necessary, with 83% receiving at least one cycle of bridging chemotherapy and 47.5% receiving at least two cycles, which is almost reminiscent of treating a patient in the third line. Median time from randomization to cell infusion was shorter in the ZUMA-7 trial (29 days) and the TRANSFORM trial (36 days) compared with the BELINDA trial (52 days), and this could be a contributing factor in explaining why patients received more cycles of bridging therapy in the BELINDA trial. The US Lymphoma CAR-T Consortium reported that patients who received bridging therapy prior to axi-cel had poorer risk factors at baseline and inferior OS.[29,30]

There were also differences in the dose of FluCy lymphodepletion, with BELINDA trial patients receiving the lowest dose; however, whether this made an impact is unknown. The end-point definition and the time point when EFS would be captured are relevant differences.

In ZUMA-7, EFS included the best response of stable disease up to 150 days (21.4 weeks), while in the TRANSFORM trial, the response assessment was captured on week 9, and in BELINDA, it was captured on week 12. More unique in the BELINDA trial was that disease response assessment or starting a new therapy before week 12 was not considered an event in either group. The initial response rates in ZUMA-7 and TRANSFORM trials were similar to their respective pivotal studies, unlike the BELINDA trial in which tisa-cel, with an ORR and CR of 42.5% and 28.4%, respectively, underperformed in comparison with the JULIET trial. There was a low percentage of patients who could proceed to auto-HCT even after achieving response (PR/CR) in the SOC arm across all three trials (64/80, 52/68, and 43/44 in ZUMA-7, BELINDA, and TRANSFORM, respectively). These data confirm the poor outcome for patients with R/R LBLC in the SOC arms. At the same time, anti-CD19 CAR-T was infused in most of the patients (94–97.8%) in the experimental arms. Crossover per protocol was allowed in both the BELINDA trial (50.6%) and the TRANSFORM trial (54.3%), whereas in the ZUMA-7 trial it was not allowed; however, patients could have received cellular therapy off protocol (56% in the SOC arm received anti-CD19 CAR-T off protocol). Despite a large percentage of patients that were able to get anti-CD19 CAR-T as a third line, ZUMA-7 and TRANSFORM showed a signal of better OS compared with SOC, and longer follow-up might further clarify this matter. In a cost-effectiveness analysis comparing axi-cel with SOC as a second-line, axi-cel was found to be cost-effective, with an improvement in quality-adjusted life-year.[31]

Cross-trial comparisons can lead to an invalid conclusion. Other limitations are that patients enrolled in clinical trials can have strict inclusion and exclusion criteria that are challenging to meet

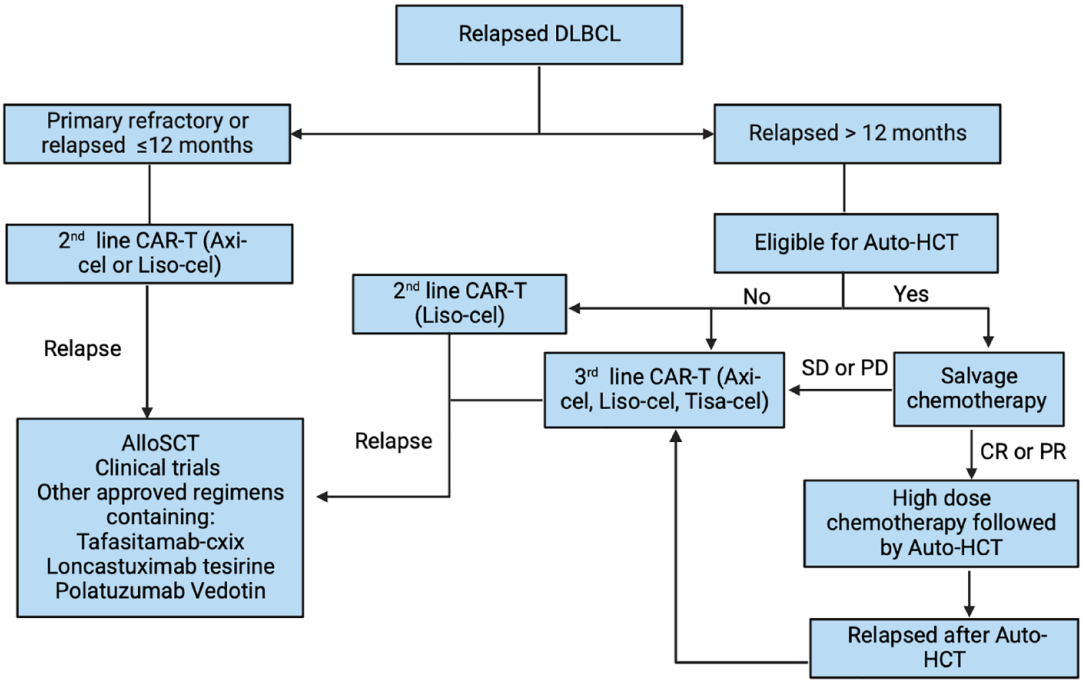

Figure 3. The changing therapeutic landscape of DLBCL in second and third line.
Auto-HCT indicates autologous hematopoietic stem cell transplant.
Axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B-cell lymphoma; Liso-cel, lisocabtagene maraleucel; Tisa-cel, tisagenlecleucel; AlloSCT, allogenic stem cell transplant.

in the general population. Another significant limitation is access to novel therapy in a specific part of the world.

The therapeutic landscape is changing rapidly in lymphoma, with recent FDA approval of anti-CD19 CAR-T in the second-line already penetrating National Comprehensive Cancer Network (NCCN) Guidelines[32] (suggested algorithm for R/R LBCL proposed in Figure 3).

Is there still a role for auto-HCT in second line or beyond?

The role of auto-HCT has been challenged by the TRANSFORM and ZUMA-7 trial results; however, we do not believe it has been completely replaced, and clinicians should carefully analyze the data when recommending anti-CD19 CAR-T therapy or auto-HCT in this setting. Recently presented PILOT study results for patients with relapse LBCL who are deemed ineligible for transplant (meeting one of the following criteria: age ⩾70 years, Eastern Cooperative Oncology Group performance status ⩾2, diffusing capacity for carbon monoxide ⩽60%, left ventricular ejection fraction <50%, creatinine clearance <60 mL/min, or alanine transaminase/aspartate transaminase > 2× upper limit of normal) and received liso-cel as a second line showed promising results with an ORR of 80% and CR of 54%, with a median duration of response of 12.1 months, and PFS of 9 months.[27] Because of the results of the PILOT study, liso-cel is also FDA approved for patients that relapse after first-line chemoimmunotherapy and are not eligible for auto-HCT due to comorbidities or age.

A registry study using the CIBMTR data looked at the outcome for patients who achieved PR as the best response, followed by auto-HCT (comparing patients with early *versus* late chemo-immunotherapy failure as defined by relapse before or after 12 months). It showed no significant difference in 5-year PFS (41% *versus* 41%) and OS (51% *versus* 63%) in late and early chemo-immunotherapy failure, respectively.[33] Another retrospective study using CIBMTR data compared auto-HCT with anti-CD19 CAR-T in relapsed DLBC for those achieving PR as the best response after salvage chemotherapy and showed no significant difference in 2-year PFS (52%

versus 42%) but reported a lower rate of relapse at 2 years (40% *versus* 52%) and superior OS (69% *versus* 46%) in auto-HCT versus anti-CD19 CAR-T, respectively.[34] These data are vital as, very often, patients will receive some chemotherapy during the waiting period of the anti-CD19 CAR-T due to logistics (e.g. insurance approval, manufacturing slots, apheresis, etc.) which is typically longer in real life than in the trial setting. The challenge will be for those patients who will respond to this second-line chemotherapy in which auto-HCT showed clear benefit. In that case, stratification based on factors may be significant. For instance, the benefit of auto-HCT in relapsed high-grade B-cell lymphoma with MYC and BCL2 rearrangements of DHL/THL seems marginal.[35]

With results of ZUMA-7 and TRANSFORM, can we expect anti-CD19 CAR-T to move to first line for LBCL?

In the ZUMA-12 trial, where axi-cel was used as first-line therapy in high-risk LBCL (DHL/THL or IPI $\geqslant$3), with an interim PET scan showing a Deauville score $\geqslant$4 after two cycles of chemoimmunotherapy, the ORR was 89%, and the CR rate was 78%.[36] With the promising results of ZUMA-12, attractive variables include the possibility of having a better quality of CAR-T cells prior to exposing lymphocytes to multiple lines of chemotherapy,[37] older patients better tolerating CAR-T over auto-HCT,[38] better managing and preventing CAR-T toxicity with corticosteroids or other maneuvers as anakinra,[39,40] utilizing more tolerable bridging therapy,[41] and avoiding the risk of secondary malignancy after high-dose chemotherapy with auto-HCT;[42] anti-CD19 CAR-T may be a safe and tolerable option in the first line for high-risk patients, but this possibility will need to be investigated further in the setting of a randomized trial.

Challenges for patients who relapse after second-line anti-CD19 CAR-T

The mechanism of relapse after anti-CD19 CAR-T remains poorly understood, and we currently do not have an SOC to salvage these patients.[30,43] However, we always encourage clinical trial participation when possible. A recent CIBMTR analysis of patients who underwent auto-HCT after three or more lines of therapy for LBCL after achieving CR/PR showed a 5-year PFS of 38% and 5-year OS of 51%. Of note, patients in this study did not receive anti-CD19 CAR-T therapy prior to auto-HCT.[44] Prolonged cytopenias after anti-CD19 CAR-T, even beyond 90 days, had been observed and not well understood. Multiple factors are thought to be contributing to prolong cytopenia, including infection, CRS, relapse, and CAR-T–related hemophagocytic lymphohistiocytosis, among others.[45,46] This can be challenging when selecting the following line of therapy, as it can be a barrier to enrolling patients in clinical trials.[43] Recognizing the above challenges and finding possible ways to overcome them will be critical to improving our CAR-T therapies. For example, an option would be to use a stem cell boost to salvage prolonged cytopenia by collecting and cryopreserving stem cells prior to CAR-T for future needs. However, this maneuver would be challenging outside of a clinical trial due to high cost, lack of insurance reimbursement, lack of available resources, and unknown feasibility of performing auto-HCT post CAR-T depending on the patient's clinical status.

What is on the horizon?

Off-the-shelf allogenic CAR-T is an exciting concept addressing logistical issues, the time needed for leukapheresis, cell manufacturing, and the quality CAR-T cells with no prior exposure to chemotherapy (as they originated from a donor without lymphoma). Multiple ongoing trials, including ALPHA (NCT03939026) and ALPHA2 (NCT04416984), use genetically modified anti-CD19 allogenic CAR products using *TALEN* gene editing and have reported promising results in early phase trials.[47,48] Other ongoing early trials include the anti-CD19 UCART019 (NCT03166878) and the CTX130 anti-CD70 allogeneic CRISPR-Cas9 (NCT04502446).[49,50] We look forward to seeing the results of the next wave of CAR-T trials currently under evaluation.

Declarations

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Not applicable.

Consent for publication

Not applicable.

Author contributions

Omar Albanyan: Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing.

Julio Chavez: Conceptualization; Formal analysis; Supervision; Writing – review & editing.

Javier Munoz: Conceptualization; Formal analysis; Supervision; Writing – review & editing.

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