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REVIEW

CAR-T CELL THERAPY. A NEW MILESTONE IN THE TREATMENT OF B-CELL LYMPHOMAS

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ABSTRACT

The outcome of patients with malignant lymphoma has significantly improved over the last decades. Major contributions have come from an increased knowledge of the disease, from its better classification, and from relevant advances in treatment. Novel important therapies have been added to the existing approach, making it possible to improve direct cancer cell killing. Further, these new therapies also support the immune system to act against the tumor, opening the era of immuno-oncology (IO). In the field of IO, chimeric antigen receptor (CAR)-T-cell therapies represent one new effective approach that has so far produced unprecedented results in the treatment of lymphomas. Four CAR-T products are available to treat relapsed refractory patients with diffuse large B-cell lymphoma (DLBCL), transformed indolent lymphoma, primary mediastinal B-cell lymphoma, and mantle cell lymphoma. Several clinical trials are currently recruiting patients to evaluate the addition of novel indications for CAR-T, to anticipate the use of CAR-T to earlier lines of treatment for DLBCL patients, and to explore combination therapies. Moreover, the CAR approach is investigated using cells other than T lymphocytes to improve feasibility and reduce the toxicity of therapy. In this review we describe the state of the art of clinical research and real-world data on the use of CAR-T, which likely represents a new milestone in the treatment of malignant lymphomas.

KEY WORDS

CAR-T; adoptive cell therapy; diffuse large B-cell lymphoma; mantle cell lymphoma; follicular lymphoma.

IMPACT STATEMENT

Clinical trials and real-world data confirm CAR-T cell therapy as a revolutionary treatment for patients with diffuse large B-cell lymphoma.

INTRODUCTION

The recent history of malignant lymphomas has been marked by a few significant milestones that have made it possible to achieve the high cure rates observed in many of the cases, confirming this group of neoplasms as one of the most curable cancers in humans. A first milestone was the introduction in the 1990s of a robust integration of pathology, immune-morphology, and molecular biology in the initial diagnosis, which was incorporated in the WHO classification of malignant hematologic malignancies (1). A second milestone was achieved with the introduction of monoclonal antibodies, and in particular of the anti-CD20 agents, which permitted the identification of novel treatment paradigms based on the use of combined immunochemotherapy programs, mainly for B-cell lymphomas, which were all associated with improved efficacy compared to the old standard chemotherapy (2-4). A third milestone was the improvement of non-invasive techniques, such as 18FDG-PET, which achieve high accuracy in the identification of the disease at different timepoints and which contributed to refining staging and response criteria, thus providing useful details for treatment personalization (5).

The current recommended treatment options obtain high response rates in around 70% of the patients with an aggressive lymphoma, such as diffuse large B-cell lymphomas (DLBCL), and mantle cell lymphomas (MCL) and in up to 90% of subjects with more indolent subtypes, such as follicular lymphomas (FL). The use of immunochemotherapy has also improved patient survival, with approximately 60% of patients with DLBCL (6) being cured and unprecedented 5-year overall survival (OS) rates of around 70-80% for other subtypes like MCL or FL (7). Although significant improvements have been achieved in most of the malignant lymphomas, there remain important unmet clinical needs that are currently challenging the entire scientific community in its search for a solution. Among current challenges, how to manage patients with refectory or relapsed disease after standard immunochemotherapy is one of the most difficult treatment decisions. This is particularly true for patients with DLBCL, who experience a dismal survival when they fail a first conventional salvage therapy (8), but this is also true for other lymphoma subtypes for which available treatment options are rapidly exhausted after second or third relapse mainly due to the lack of active agents. In this setting of very high-risk patients with no active conventional options, the use of cellular therapy is emerging as a promising approach with positive results in hard-to-treat patients. Chimeric antigen receptor (CAR) T-cell therapies have proved effective and are currently registered for the treatment of DLBCL patients who relapse after high dose salvage therapy and will soon be registered for the treatment of high risk relapsed patients with MCL or FL as well. The possibility of achieving a cure in a significant proportion of patients lacking other therapeutic choices has shed light on this novel treatment modality, which merits becoming a new milestone in the treatment of malignant lymphomas and which may represent a significant improvement in the future treatment of other cancers. In this review we describe the main characteristics of CAR-T cell therapies and the main results achieved in malignant lymphomas. We also discuss the future development of CAR-T use in lymphomas.

CAR-Ts AND CAR PRODUCTS

CAR-T therapies, one of the most advanced tools of cellular-based cancer treatment, were developed thanks to the landmark experiments that defined the structure/function of the T-cell receptor (TCR) and evaluated adoptive cell therapies with tumor-infiltrating lymphocytes. The first genetically engineered T cell expressing a 1st generation CAR, which contained the variable antigen-recognition domains of an antibody linked to the constant transmembrane and intracellular CD3-zeta signaling domains of a TCR, was published in 1987 by

Yoshihisa Kuwana *et al*. (9). However it took nearly 20 years to successfully move the first CAR-T from the bench to the bedside and to improve transduction efficiency, CAR-T activation, and expansion and CAR construct optimization. The clinical development of CAR-T quickly moved to a 2nd generation CAR, which contains the addition of either a CD28 or 41BB intracellular co-stimulatory domain to augment CD3-zeta-mediated intracellular signaling and optimize T cell activation (10). In 2017, the pivotal ZUMA-1 trial evaluating axicabtagene ciloleucel, the 2nd generation CD19-targeted CAR-T cell product, demonstrated the remarkable efficacy of CD19 CAR-T cell therapies in relapsed refractory DLBCL and led to the first US FDA approval of a CAR-T therapy in this setting (11). Since then, additional 2nd generation CD19 CAR-T products for B-cell lymphoma, including tisagenlecleucel (12), brexucabtagene autoleucel (13), and lisocabtagene maraleucel (14) , have become available (**table I**).

Despite the high activity observed for CD19 CAR-T therapies in the pivotal studies, this treatment is associated with a unique safety profile, with potentially life-threatening toxicities including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) (15). CRS is associated with elevated serum levels of pro-inflammatory cytokines, including interferon gamma (IFN-gamma), TNF, IL-6, and IL-10, which contribute to a systemic hyperinflammatory syndrome characterized by fever, hypotension, and hypoxemic respiratory failure (16). The pathophysiologic mechanism of ICANS is likely related to an underlying endothelial dysfunction, leading to a leakage of elevated serum cytokine levels across the blood–brain barrier, thereby causing an inflammatory encephalopathy (17, 18). Considered together, the production of the CAR-T and the management of the patient during CAR-T therapy represent important challenges for clinical management.

CAR-T CELL STUDIES IN LYMPHOMAS

Phase II studies are available that describe the clinical activity and safety profile of the four CAR-T compounds.

The efficacy of axi-cel was demonstrated in the ZUMA-1 trial, published in 2017 and updated in 2019 (11, 19). The trial enrolled 111 patients with relapsed/refractory (r/r) DLBCL, primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (tFL); of the enrolled patients, 101 received axi-cel infusion and 108 were included in the final evaluation. Bridging therapy was not allowed. The overall response rate (ORR) was 82%, with a complete response (CR) rate of 54%. Most of the responses were observed within six months from infusion, and the probability of response was correlated with CAR-T expansion within the first 28 days. The most recent study update, with 27.1 months of follow-up, demonstrated a median duration of response (DOR) of 11.1 months for all patient, with median DOR not reached for CR patients. Similarly, median OS was not reached, while median PFS was 5.9 months.

Regarding the safety profile, axi-cel treatment was associated with adverse events (AE) of any grade in 95% of the patients, hematologic events being the most frequent (neutropenia 78%, anemia 43%, and thrombocytopenia 38%). Ninety-three percent and 64% of the patients experienced CRS and ICANS of any grade, respectively. Severe CRS and ICANS occurred in 13% and 28%, respectively. Overall, three out of 44 deaths were referred as non-relapse events. Tocilizumab was used in 43% of patients with CRS and/or ICANS; corticosteroids were used in 27% of the entire cohort of patients. The efficacy of axi-cel was also demonstrated for patients with indolent lymphomas who were relapsed or refractory to at least two prior lines of therapy. As of 3 December 2020, 146 patients (124 FL; 22 MZL) received axi-cel. Patients had a median of three prior lines of therapy. With a median follow-up of 17.5 months, the ORR was 92%, with a 76% CR rate. In patients with FL (n = 84), the ORR was 94% (80% CR rate). The medians for DOR, PFS, and OS were not reached. The safety profile of the study was similar to that observed in the ZUMA1 trial (20).

The efficacy of tisa-cel was demonstrated in the JULIET trial initially published in 2019 (12) and was updated in 2020 and again in 2021 (12, 21). The trial enrolled 165 patients with DLBCL, tFL, and high-grade B-cell lymphoma (HGBCL) refractory or relapsed after two or more lines of therapy; 111 patients received tisa-cel infusion, and 93 were included in the final evaluation. The study allowed bridging therapy, which was used in 92% of the cases. The overall ORR was 52%, with a CR rate of 40% The most recent update of the study, with 60.7 months of follow-up, showed an ORR of 58%, with a CRR of 46%, and a median DOR of 61.4 months in patients with DLBCL. Regarding the safety profile, tisa-cel treatment was associated with grade 3-4 AE in 85% of the patients,

	AXICABTAGENE CILOLEUCEL	TISAGENLECLEUCEL	LISOCABTAGENE MARALEUCEL
Pivotal Trial	ZUMA-1(11) Phase I/II	JULIET (12) Phase II	TRANSCEND(14) Phase II
CAR Construct	α CD19 2nd gen, CD28	α CD19 2nd gen, 41BB	α CD19 2nd gen, 41BB
Leukapheresis	Fresh product direct to manufacturing (within US)	Cryopreserved product (could be stored before manufacturing)	Fresh product direct to manufacturing (within US)
Study Population	111 enrolled; 101 dosed 76% DLBCL; 16% tFL; 8% PMBCL 79% refractory 21% post-ASCT	165 enrolled; 111 dosed 80% DLBCL; 18% tFL 54% refractory 49% post-ASCT	344 enrolled, 269 dosed 51% DLBCL, 13% HGBCL, 6% PMBCL, 1% FL grade 3b 67% refractory 35% post-ASCT
CNS disease	No history of, or active, CNS disease allowed	No active CNS disease allowed	Secondary CNS involvement allowed
Patients receiving bridging therapy	Not allowed	92%	59%
Lymphodepleting Chemo	Flu 30 mg/m2 and Cy 500 mg/m2 on Days -5, -4, and -3	Flu 25 mg/m2 and Cy 250 mg/m2 on Days -5,-4, and -3 Bendamustine 90 mg/m2 daily for 2 days	Flu 30 mg/m2 and Cy 300 mg/m2 X 3 days, 2–7 days before infusion
CAR-T Dose	2.0 X 106 CAR-T cells/kg If > 100 kg, max. 2.0 X 108 CAR-T cells	Median, 3 x 108 CAR-T cells Range, 0.1-6.0 X 108 cells	DL1: 50 x 106 CAR-T cells (n = 45) DL1: 100 x 106 CAR-T cells (n = 183) DL3: 150 x 106 CAR-T cells (n = 41) (CD4:CD8 in 1:1 ratio)
Prior anti-CD19 therapy	Not allowed	Not allowed	Allowed, if CD19+ tumor present
Efficacy	OR: 82% CR: 54% Med. DOR: 11.1 mo. Med. PFS: 5.9 mo. OS at 18 mo.: 52%	OR: 52% CR: 40% Med. DOR: NR at 17 mo. Med. OS: 11.1 months	OR: 61% CR: 44% Med. DOR: NR at 12 mo. Med. PFS: 6.8 mo. Med. OS: 21.1 mo.
Safety	CRS: All grades: 93% ≥ Grade 3: 13% Neurotoxicity: All grades: 64% ≥ Grade 3: 28% Grade 5 AEs: 6%	CRS: All Grades: 58% ≥ Grade 3: 22% Neurotoxicity: ll grades: 21% ≥ Grade 3: 12% Grade 5 AEs: 3%	CRS: All Grade: 42% ≥ Grade 3: 2% Neurotoxicity: All grades: 30% ≥ Grade 3: 10% Grade 5 AEs: 0%

Table I. *Characteristics of available CAR-T products for the treatment of DLBCL.*

US: United States; FDA: Food and Drug Administration; gen: generation; DLBCL: diffuse large B-cell lymphoma; tFL: transformed follicular lymphoma; ALL: acute lymphoblastic leukemia; PMBCL: primary mediastinal B-cell lymphoma; MCL: mantle cell lymphoma; post-ASCT: post-autologous stem cell transplantation; chemo: chemotherapy; Flu: fludarabine; Cy: Cyclophosphamide; CAR-T: chimeric antigen T-cell; yrs: years; kg: kilogram; max: maximum; DL: dose level; CNS, central nervous system; OR: overall response; CR: complete response; Med.: median; DOR: duration of response; PFS: progression-free survival; OS: overall survival; mo.: months; CRS: cytokine release syndrome; AE: adverse event.

hematologic events being the most frequent (neutropenia 34%, anemia 48%, and thrombocytopenia 33%). Fifty-eight percent and 21% of the patients experienced CRS and ICANS of any grade, respectively. Severe CRS and ICANS occurred in 22% and 12%, respectively. No death was recorded as a non-relapse event. Tocilizumab was used in 14% of patients with CRS and/or ICANS; corticosteroids were used in 10% of the patients.

In the ELARA phase II study the activity of tisa-cel

was demonstrated in r/r FL within 6 months after second-/later-line therapy (22). As of May 26, 2020, 122 pts had been screened, 98 were enrolled, 97 received tisa-cel (median follow-up: 6.5 months), and 52 were evaluable for efficacy (median follow-up: 9.9 months). The median number of prior lines of therapy was four. CRR was 65.4% in the intention-to-treat (ITT) population and ORR was 82.7%. Median DOR, PFS, OS, and time to next anti-lymphoma treatment were not reached. Grade ≥ 3 AE were observed in 69% of patients, with a similar toxicity profile to that of the Juliet trial.

The efficacy of liso-cel was demonstrated in the TRANSCEND trial, published in 2020 (14). Differently from the other products, liso-cel is the only agent with a fixed 1:1 ratio of CD4/CD8 transduced and infused T cells. The study enrolled 344 patients with DLBCL, tFL, HGBCL, and FL grade 3B refractory or relapsed after two or more lines of therapy; 269 patients received liso-cel infusion, and 256 were included in the final evaluation. The study allowed bridging therapy, which was used in 59% of the cases. The overall ORR was 73%, with a CR rate of 53%. With 18.8 months of follow-up, the median DOR was not reached; median PFS and OS were 6.8 and 21.1 months, respectively.

Regarding the safety profile, liso-cel treatment was associated with AE of grade 3 or higher in 79% of the patients, hematologic events being the most frequent (neutropenia 60%, anemia 37%, and thrombocytopenia 27%). Forty-two percent and 30% of the patients experienced CRS and ICANS of any grade, respectively. Severe CRS and ICANS occurred in 2% and 10%, respectively; however, seven patients (3%) experienced non-relapse mortality. Tocilizumab or glucocorticoids were used in 20% of patients. Overall, no correlation was observed in the ZUMA-1, JULIET, and TRANSCEND trials between efficacy outcomes and age, DLBCL cell of origin, prior therapies, or use of steroids or tocilizumab. Nonetheless, high baseline tumor burden and high baseline pro-inflammatory markers were associated with lower treatment efficacy.

The efficacy of brexu-cel for the treatment of relapsed refractory mantle cell lymphoma was demonstrated in the ZUMA-2 trial, published in 2020 (13). The trial enrolled 74 patients with MCL refractory or relapsed after two or more lines of therapy, of whom 68 received brexu-cel infusion, and 60 were included in the final evaluation. Based on the intention-to-treat analysis, ORR was 85% and CRR was 59%. With 12.3 months of follow-up, 57% of the patients remained in remission, with an 83% 1-year OS and with a 1-year PFS of 61%. An ongoing confirmatory study is currently recruiting patients (NCT04880434).

Regarding the safety profile, brexu-cel was associated with AE of grade ≥ 3 in 99% of the patients, hematologic events being the most frequent (neutropenia 34%, anemia 48%, and thrombocytopenia 33%). Ninety-one percent and 63% of the patients experienced CRS and ICANS of any grade, respectively. Severe CRS and ICANS occurred in 15% and 31%, respectively. Tocilizumab was used in 59% of patients with CRS and/or ICANS; corticosteroids were used in 38% of the patients.

REAL-WORLD STUDIES ON CAR-T

The results of the above-mentioned pivotal trials led to the FDA's approval of the three products for the treatment of adult patients with r/r DLCBL, tFL, HGBCL, PMBCL (axi-cel and liso-cel only), and FL grade 3b (liso-cel only). The European Medical Agency (EMA) has so far approved only axi-cel and tisa-cel, with the same indications as in the US. More recently, the FDA approved the use of brexu-cel for the treatment of relapsed refractory MCL and axi-cel for the treatment of r/r FL.

Since FDA approval, several investigators have reported real-world studies (RWS) on the approved indications of CAR-T cell therapies in patients with aggressive lymphomas both in the US and in Europe. (see **table II** and **table III**).

A consortium of 17 institutions in the United States, the US Lymphoma CAR-T Consortium, performed a retrospective analysis evaluating the clinical outcomes of 298 patients treated with standard-of-care (SOC) axi-cel for r/r DLBCL (23). Patients had a median age of 60 years (range, 21-83 years). This included patients with poor PS, ECOG score 2-4 (19.5%), disease stage III-IV (82.4%), and international prognostic index (IPI) score 3-5 (54.4%). In the real world, axi-cel was used in patients with DLBCL (68.1%), PMBCL (6.4%), and tFL (25.5%). Of these, 22.8% had double- or triple-hit lymphoma, and 37.4% were double expressors.

Over half of the patients (53%) received bridging therapy (BT) of any kind showed worse OS than those who did not require BT. The poorer outcome associated with BT may be a result of pretreatment factors rather than the result of the BT alone. An interesting observation was made for patients who

	AXICABTAGENE CILOLEUCEL			TISAGENLECLEUCEL		
	Nastoupil *et al*. (23) (N = 298)	Jacobson *et al*. (24) CIBMTR (N = 1001)	Riedell *et al*. (26) (N = 149)	Pasquini *et al*. (25) CIBMTR (N = 155)	Riedell *et al*. (26) (N = 75)	Iacoboni *et al*. (30) (N = 91)
Histology, %						
DLBCL	68	-	86	-	94	73
tFL	26	28	-	27	-	23
PMBCL	6	-	-	-	-	-
Other	0	-	-	-	-	4
Median age, years (range)	60 (21-83)	62 (-)	58 (18-85)	65 (18-89)	67 (36-88)	60 (52–67)
Patients ≥ 65 years, %	52[a]	37	-	53	-	31
HGBCL/double/triple hit, %	23	14	-	11	-	15
Refractory/resistant to last line of therapy, %	42	62	-	-	-	29
ECOG PS, % 0-1	80	83	86	83	94	88
Previous autoSCT, %	33	29	29	26	23	39
Previous lines of therapy, median (range)	3 (2-11)	-	3 (2-11)	4 (0-11)	4 (2-9)	3(2-4)
≥ 3, %	75	-	-	-	-	28[b]
Received bridging therapy, %	53[c]	-	61	-	72	87
CR - PR, %	64 - 18	53 - 17	43 -	40 - 22	44 -	32 - 28
Median follow-up, mo.	12.9	12	-	11.9	-	14,1

Tables II. *Comparison of real-world data between axicabtagene ciloleucel and tisagenlecleucel.*
[a] Patients ≥ 60; [b] > 3 prior lines of therapy ; [c] bridging therapy included chemotherapy (54%), steroids only (23%), radiation therapy (12%), and targeted regimens (10%).

received radiotherapy as BT, which may result in improved PFS when compared with systemic therapy in select patients. Despite differences in the baseline characteristics of patients prescribed with SOC axi-cel, similar rates of toxicities were observed in comparison to ZUMA-1; CRS of any grade occurred in 91% of patients; 7% developed grade 3 or higher CRS, and one patient died as a result of HLH. Neurotoxicity occurred in 69% of patients, with grade 3 or higher occurring in 31%. One patient developed grade 5 cerebral edema. Tocilizumab and corticosteroids were given to 62% and 54% of patients, respectively, for CRS, neurotoxicity, or both.

Two real life studies were generated from the database of the Center for International Bone Marrow Transplant Research (CIBMTR). A first study was published on 1001 patients treated with axi-cel and observed for a median follow-up of 12 months (24). The median age of treated patients was 62 years, with 37% aged 65 or older. Twenty-eight percent had transformed lymphoma, and 14% high-grade lymphoma. The best ORR was 70% (CR 53%). The ORR, CR, 12-month PFS, and OS were 78% *vs* 66%, 60% *vs* 48%, 55% (95% CI, 48-62%) *vs* 40% (95% CI, 37-44%), and 70% (95% CI, 63-76%) *vs* 54% (95% CI, 50-58%), for chemosensitive and chemoresistant disease, respectively. The incidence of CRS grades ≥ 3 according to American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading was 13%. ICANS were reported in 57% patients, with 26% of grade 3 or higher.

A second study was published on 155 patients treated with tisa-cel, reporting ORR and CR rates of 61.8% and 39.5%, respectively, which were very similar to those reported in the JULIET study (25). The median age was 65 years (range 18-89); 17 patients (11%) had double- or triple-hit features, and 27% had tFL. Any grade CRS occurred in 45%, grade 3 or higher occurred in 4.5%. Any grade ICANS occurred in 18%, grade 3 or higher occurred in 5.1%. The ORR was 62%, including the 40% achieving CR. Tocilizumab and corticosteroids were adminis-

AXICABTAGENE CILOLEUCEL + TISAGENLECLEUCEL				
	Chiappella *et al.* (28) SIE registry N = 113	Ghafouri *et al*. (45). N = 53	Le Gouill (29), DESCAR-T registry N = 550[c]	Dreger *et al.* (27) N = 267
Infused axi, n	59	45	350	137
Infused tisa, n	54	8	200	130
Histology, % DLBCL tFL PMBCL Other	 68 12 20 -	100 - - - -	 88 4 8 -	-
Median age, years (range) Patients ≥ 65 years, %	53 (19-70) -	63 (18-82) 60[a]	63 (18-79) 44	-
HGBCL/double/triple hit, %	16	14	1.7	-
Previous autoSCT, %	29	9	21	-
Previous lines of therapy, median (range) ≥ 3, %	3(2-7)	3(1-6) 32[b]	3 (1-10)	-
Received bridging therapy, %	86	58	82	79%
Patients who received CAR-T cells, (%)	100	100	100	100
ORR: CR - PR, %	40 - 31	64 - 8	53 - 21.2	Axi: 40 – 37 Tisa: 25 - 22
Median follow up, months	6,9	15,2	6.5	6.7

Tables III. *Comparison of real-world data between axicabtagene ciloleucel and tisagenlecleucel.*

[a] ≥ 60 years old; [b] ≥ 4; [c] data about patients who underwent leukapheresis

CIBMTR: center for International Blood and Marrow Transplant Research; DLBCL: diffuse large B-cell lymphoma; tFL: transformed follicular lymphoma; PMBCL: primary mediastinal B-cell lymphoma; HGBCL: high-grade B-cell Lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; autoSCT: autologous stem cell transplant; CAR-T: chimeric antigen T-Cell; ORR: objective response rate; CR: complete response; PR: partial response rate; SIE: Società Italiana di Ematologia.

tered in 43% and in 10%, respectively.

Riedell *et al.* reported on 149 patients treated with axi-cel and 75 treated with tisa-cel at eight academic medical centers in the United States (26). Most patients were DLBCL with favorable PS and a median age of 58 years for axi-cel and 67 for tisa-cel. At day 90, the CR rate was 39% both for axi-cel and tisa-cel. Real-world data do not currently exist for liso-cel owing to its very recent approval.

Authors from the German Register for Stem Cell Transplantation (DRST) presented a first risk factor analysis of standard-of-care (SOC) CAR-T cell therapies for DLBCL(27). A total of 267 patients were included, who received axi-cel (137) or tisa-cel (130) for treatment of DLBCL until December 2020. Compared to the approval trials, patients were at relatively higher risk. Both CRS and neurotoxicity were significantly more common after axi-cel than after tisa-cel. Overall and complete response rates to axi-cel and tisa-cel were 77% and 47% (p < 0.0001), and 40% and 25% (p = 0.013), respectively. With a median follow-up of 6.7 months, progression/relapse occurred in 52% and 72% patients after axi and tisa-cel, respectively (p = 0.0027). Other significant risk factors for PFS on univariable analysis were elevated LDH, need for bridging therapy, and > 3 pretreatment lines. The adverse impact of tisa-cel, LDH, and bridging on PFS remained significant after multivariable adjustment for confounders (HR 1.51 (95% CI, 1.12-2.04), 1.55 (1.1-2.18), and 1.66 (1.12-2.46), respectively).

The Italian Society of Hematology (SIE) reported the results of a prospective RWS on 113 patients who were infused with axi-cel (59) or tisa-cel (54). The median age was 53 years (19-70); 52% of patients had DLBCL, 16% high-grade HGBCL, 20% PMBCL, and 12% tFL. Bridging therapy was delivered to 86% of patients. The median follow-up for infused patients was 6.9 months. CRR was 40% and ORR 71%. For the evaluable patients, DOR was 58% at

12 months. No differences between axi-cel and tisa-cel were reported. Grade 3-4 CRS was observed in only 5% of patients and severe ICANS in 10%. No toxic deaths were recorded(28).

In a similar study, Le Gouill *et al*. performed a retrospective analysis of patients in France treated with axi-cel or tisa-cel between April 2018 and March 2021 (29). A total of 550 patients were identified who received axi-cel (350) or tisa-cel (200). The median age was 63 (range 18 -79); 482 patients had DLBCL and 21 PMBL. The median number of prior lines was three, and 21% of patients had a prior ASCT; 80.2% received a bridging therapy. The median time between the CAR-T order and its infusion was 50 days (range 43 to 60 days). Response was available in 419 infused patients. Best ORR was 70.2%. At day 30 after CAR-T (D30) cell infusion, 38% patients achieved CR and 27% achieved PR. Among CR patients at D30 (157), 61% remained in CR at D90. The median follow-up was 7.4 months. The median OS calculated from time of CAR-T infusion was 12.7 months.

Iacoboni *et al*. reported the real-world experience with tisagenlecleucel in ten Spanish institutions (30). Of the 91 patients who underwent leukapheresis, 82% received tisa-cel therapy. The median age was 60 years; 58% of patients had DLBCL, 23% had tFL, and 15% had HGBCL; 87% received bridging therapy before infusion. The median time from apheresis to infusion was 53 days. The median follow-up from CAR-T cell infusion was 14.1 months. ORR and CR were 60% and 32%, respectively. Among the infused patients, 15% developed any grade of ICANS. Tocilizumab and steroids were administered to 32% and 21% of patients, respectively.

ONGOING TRIALS OF CD19 CAR-T CELL

The results of the phase II trials have paved the way for a wide range of studies aimed at four different main goals: increasing treatment safety, improving outcomes in the already addressed population, evaluating the potentialities of CAR-T cell therapies in the second line of treatment, and investigating CAR-T cells potentialities in other categories of patients (**table IV**).

Regarding the first goal, new strategies are currently being evaluated to lower the incidence and severity of CRS and ICANS through the use of JAK1 inhibitors such as itacitinib (NCT04071366), interleukin receptor antagonists (NCT04150913), or by introducing granulocyte-macrophage colony-stimulating factor antagonists such as lenzilumab (ZUMA-19, NCT04314843).

Regarding the second, the improvement of CAR-T cell efficacy in the relapsed/refractory DLBCL setting after second-line treatment is currently pursued through ongoing studies associating CAR-T with other drugs, such as acalabrutinib (NCT04257578), atezolizumab (ZUMA-6 study, NCT 02926833), and durvalumab or ibrutinib (PLATFORM trial, NCT03310619).

Three main studies are evaluating the efficacy of CAR-T cell in r/r DLBCL after first-line treatment by comparing cellular therapy to standard salvage chemotherapy (SOC) followed by autologous stem cell transplantation. These three studies, BELINDA, ZUMA-7, and TRANSFORM, which are evaluating tisa-cel, axi-cel and liso-cel, respectively, have shown promising preliminary results, with ZUMA-7 and TRANSFORM having reached the primary endpoint by demonstrating an event-free survival (EFS) advantage in the CAR-T cell arm. More precisely, ZUMA-7 trial randomized 359 patients in a 1:1 ratio between axi-cel and SOC, outlining an increased CR rate (65% *vs* 32%) and EFS (8.3 months *vs* 2 months) (31). Of note, bridging therapy was not permitted in accordance with the previous ZUMA-1 trial. Analogously, the TRANSFORM trial compared liso-cel with SOC, demonstrating advantages in the CAR-T cell arm in terms of CR rate (66% *vs* 39%, $p < 0.0001$) and EFS (10.1 months *vs* 2.3 months, $p < 0.0001$) (32). On the other hand, Belinda trial comparing tisa-cel with SOC failed to meet its primary endpoint (EFS). Among 322 randomized patients, ORR at week 12 was 46% in experimental arm and 43% in observational arm (33).

Regarding the fourth goal, several studies are investigating CAR-T cell therapies in different patient cohorts and different B-cell neoplasms. Among them, LYSARC (the Lymphoma Academic Research Organisation, NCT04531046) is evaluating axi-cel as a second-line therapy in unfit patients, while the BIANCA trial (NCT 03610724) is investigating tisa-cel in children and young adults with DLBCL. The ZUMA-12 trial (NCT03761056), another phase II study assessing axi-cel in high-risk DLBCL patients with suboptimal interim response to first-line therapy, showed promising preliminary results, with a CR rate of 80% and EFS not reached after a median follow-up of 15.9 months. Among trials that are investigating the efficacy of CAR-T cell therapy in other B-cell neoplasms, the TARMAC trial is evaluating a combination of tisa-cel and ibrutinib in

TRIAL NAME (NCT NUMBER)	INDICATION	DRUGS	PHASE	LINE OF THERAPY
ZUMA-12 (NCT03761056)	High risk DLBCL	Axi-cel	2	1st
NCT04531046	Transplant ineligible r/r aggressive B-cell NHL	Axi-cel	2	2nd
TIGER-CTL019 (NCT04161118)	Transplant ineligible r/r aggressive B-cell NHL	Tisa-cel	2	2nd
TRANSCENDWORLD (NCT03484702)	r/r aggressive B-cell lymphoma	Liso-cel	2	≥ 2nd
NCT04608487	r/r aggressive B-cell lymphoma with primary or secondary CNS involvement	Axi-cel	1	≥ 2nd
NCT04257578	B-cell NHL	Axi-cel + Acalabrutinib	1-2	≥ 3rd
ZUMA-6 (NCT02926833)	Refractory DLBCL	Axi-cel + Atezolizumab	1-2	≥ 3rd
ZUMA-19 (NCT04314843)	r/r DLBCL	Axi-cel + Lenzilumab	1-2	≥ 3rd
NCT05077527	r/r HIV-associated aggressive B-cell NHL	Axi-cel	1	≥ 3rd
PLATFORM (NCT03310619)	r/r DLBCL	Liso-cel + Durvalumab or CC-122	1-2	≥ 3rd
TRASCEND-OUTREACH-007 (NCT03744676)	r/r DLBCL or FL 3b	Liso-cel, outpatient setting	2	≥ 3rd
NCT03876028	r/r DLBCL	Tisa-cel + Ibrutinib	1b	≥ 3rd
TARMAC (NCT04234061)	r/r MCL	Tisa-cel + Ibrutinib	2	≥ 2nd
TRANSCEND FL (NCT04245839)	r/r FL (grades 1-3a) or MZL	Liso-cel	2	≥ 2nd
NCT03331198	r/r CLL or SLL	Liso-cel + Ibrutinib/ Venetoclax	1-2	≥ 3rd

Table IV. *Ongoing clinical trials exploring further applications of approved CAR-T cell products in adult B-cell lymphomas.*
DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin lymphoma; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; FL: follicular lymphoma; CLL: chronic lymphocytic leukemia; SLL: small lymphocyte lymphoma.

mantle cell lymphoma (NCT 04234061) and TRANSCEND FL (NCT04245839) is investigating CAR-T therapies in follicular lymphoma. Also, the TRANSCEND-CLL-044 is assessing CAR-T cell therapy in chronic lymphocytic leukemia/small lymphocytic lymphoma (NCT03331198).

FUTURE OF CAR TECHNOLOGY

The advent of CAR-T cell therapies has dramatically improved outcomes in the relapsed/refractory setting of several lymphoma subtypes. However, refractoriness to CAR-T treatment, relapse after initial response, therapy-related toxicities, and treatment costs represent relevant hurdles to overcome (34).

Therefore, several research fields are being developed towards different aims: to identify strategies to increase CD-19 CAR-T activity and persistence, to target new antigens in B-cell neoplasms, and to identify alternative platforms for CAR engineering. Overall, the optimization of CD-19 CAR-T function is mainly pursued in three different ways. First, through the co-administration of drugs capable of hindering immune escape such as programmed death protein 1 inhibitors (PORTIA trial, NCT03630159) or drugs able to stimulate T cell expansion (*e.g.*, interleukin-7 receptor agonists). Second, through the employment of CRISPR-Cas9 gene editing to e ndow CAR-T cells with the ability to counteract tumor-dependent immunosuppressive signals like TGF-β (35, 36). Third, through the modification of CAR construct by introducing additional co-stimulatory domains (3rd generation CAR-T cells) or additional endodomains capable of inducing stimulatory cytokines production (4th generation) (10).

Although CD19 represents an ideal target for CAR-T cells because it is expressed uniformly at high site density on B-cell malignancies, targeting a single antigen in cancer is fraught with the potential for antigen loss variants to emerge. Therefore, new targets are sought in order to hamper this phenomenon. Among them, CD20 and CD22 represent the most promising targets thanks to their uniform presence and persistence in B-lymphoid cells (37). Several phase I-II trials with CD20 or CD22 CAR-T cells are ongoing (*e.g.*, NCT03277729). Among other B-cell receptor targets, CAR-T cells directed against CD79a, CD37, and BAFF-R are currently under development.

The immune escape through antigen drop can also be overcome through multiple antigen targeting. Three different techniques are being tested in order to pursue this aim: 1) the co-administration of two or more CAR-T cell lines, with each line expressing a different antigen specificity; 2) the co-transduction of T-cells with two vectors encoding the two separate CARs (bi-specific CAR-T, NCT04007029); 3) T-cell engineering with only one vector encoding both CARs (bicistronic CAR-T) (38). The latter strategy may lead to a less expensive and more homogeneous product and is therefore regarded as a very promising approach.

The development of new CAR-T cell therapies with enhanced efficacy and wide target range will probably lead to a broader application in hematology-oncology. Manufacturing time and costs represent therefore a substantial limitation to the use of CAR-T, which must be overcome. In order to pursue this aim, several efforts are directed towards the identification of alternative vehicles for CAR engineering that can be manufactured and stored to be readily available, with reduced costs and waiting time. Allogeneic CAR-T cells represent one of the most promising approaches. T lymphocytes obtained from peripheral blood mononuclear cells from healthy donors, umbilical cord blood, or derived from induced pluripotent stem cells undergo a gene editing process able to confer resistance to host rejection and independence from major histocompatibility complex (MHC) for T cell activation, and are also able to avoid graft-versus-host reaction (GVHD) (39). These so-called "off-the-shelf" universal CAR-T (U-CAR-T)(40) are currently in the early phase of clinical development (*e.g.*, NCT04264039). Another promising CAR vehicle is represented by natural killer (NK) cells, which, unlike T cells, can kill transformed cells without the need for prior antigen priming and without MHC restriction. Moreover, allogeneic NK cells do not induce GVHD. NK cells can be derived from autologous or allogeneic sources and can be propagated *in vitro* (41-43). A first-in-human phase I-II trial employing CAR-NK cells in r/r B-cell malignancies, with promising results, has been published. A third source of alternative CAR vehicles is represented by cytokine-induced killer cells (CIK), immune effector cells featuring a mixed T and NK cell phenotype that can kill both in an MHC-dependent and -independent manner. This approach is currently being evaluated in B-cell acute lymphoblastic leukemia (44).

Lastly, other ongoing trials may influence the future of CAR-T cell therapies by broadening their use and lowering therapeutic costs. These trials focus on the development of CAR-T management regimens that may allow outpatient administration. Recruiting trials are available for liso-cel (TRASCEND-OUTREACH-007, NCT03744676) and axi-cel (NCT05108805).

CONCLUSIONS

In conclusion, the available data on the efficacy of CAR-T therapies and the numerous planned and recruiting clinical trials confirm this novel treatment modality as a new milestone for the treatment of lymphomas. The use of CAR-T has already made it possible to treat several patients around the world and to cure a significant proportion of subjects lacking other effective alternative options. Real-world data are reassuring about the possibility of moving a complex treatment modality from the bench of clinical trials to the bedside of our patients. The science of CAR-T, and more in general that of adoptive cell therapies, has gained momentum as one of the most promising approaches to the treatment of cancer in humans and will likely impact the near future of oncology.

ETHICS

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Conflict of interests

Prof Stefano Luminari has had a role as advisor for the following companies: Roche, Jannsen, Gilead/kite, BMS/Celgene, Regeneron, Genmab, and Abbvie.

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Authors' contribution

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Ethical approval

N/A.

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