Anti-CD19 chimeric antigen receptor T-cell therapy in B-cell lymphomas: current status and future directions

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Aims: To review recent data and relevant of the role of anti-CD19 chimeric antigen receptor (CAR) T-cell therapy for B-cell non-Hodgkin lymphoma (NHL). **Methods:** Review and compilation of the most recent and relevant data published in full text and abstract forms of anti-CD19 CAR T-cell therapy for B-cell NHL. **Results:** Different anti-CD19 CAR T-cell therapy products have been tested and shown significant clinical activity across B-cell NHL patients. The objective responses in relapsed DLBCL, FL and MCL were 50–83%, 83–93% and 93%, respectively. **Conclusions:** Anti-CD19 CAR T-cell therapy is a viable option for poor risk refractory B-cell NHLs.

Non-Hodgkin lymphoma (NHL) accounts for 4% of all neoplastic disorders [1]. An estimated 77,240 new cases of NHL were anticipated in 2020; unfortunately, 19,940 deaths would still occur [1]. NHLs encompass a heterogeneous spectrum of lymphoid malignancies, mostly (85%) arising from B lymphocytes [2,3].

Diffuse large B-cell lymphoma (DLBCL) is the most common type among B-cell lymphomas, accounting for one-third of cases [4]. It is characterized by a rapidly growing lymphadenopathy, typically presenting with advanced stages and extranodal disease [5,6], with one-third reporting B symptoms [4]. Relapsed DLBCL after standard front-line chemoimmunotherapy are generally offered salvage therapy followed by autologous hematopoietic cell transplantation (auto-HCT) if chemosensitive disease [7–9]. Outcomes of refractory DLBCL after second-line or auto-HCT are poor [10,11].

US FDA approval of anti-CD19 chimeric antigen receptor T (CAR T)-cell therapy for R/R DLBCL constituted a breakthrough in immunooncology. In the ZUMA-1 study, axicabtagene ciloleucel (axi-cel; Yescarta®, Kite A Gilead company, CA, USA), yielded remarkable objective response rate (ORR) of 82% and complete remission (CR) of 54% [12]. Axi-cel is approved for DLBCL after failure of two or more lines of systemic therapy, including DLBCL, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma and transformed follicular lymphoma [13]. Similarly, tisagenlecleucel (tisa-cel; Kymriah®, Novartis, NJ, USA), another anti-CD19 CAR T-cell therapy, was FDA approved in May 2018 for all aforementioned indications except PMBCL [14].

Follicular lymphoma (FL) is the second most common lymphoma in the USA and other Western countries. Although it is considered an indolent and incurable disease, its prognosis has improved in the rituximab era with a 10-year overall survival rate (OS) of 80% [15]. In symptomatic FL patients, the standard frontline therapies continues to evolve, from anti-CD20-based chemotherapy regimens to chemotherapy-free options [16,17]. Several scoring systems have been developed using clinical, laboratory and molecular/genomic variables that predict survival outcomes with high-risk subgroups having a %-year OS between 25 and 60% [18–20]. However, the strongest predictor of OS in FL is disease progression within 2 years of completing chemoimmunotherapy (POD24) with a OS of 50% at 5 years, independent of the FLIPI score [21]. The treatment landscape of relapsed FL has seen significant advances with the introduction of PI3K inhibitors (idelalisib, copanlisib and duvelisib) [22,23]. Tazemetostat is novel drug

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that targets EZH2 is also FDA approved for R/R FL currently [24]. Despite these advances, FL continues to be considered an incurable disease and patients are expected to relapse.

Mantle cell lymphoma (MCL) is a rare subtype of NHL designated as an orphan disease, accounting for 5% of all lymphomas in the USA. Most patients present with advanced stages and extranodal disease [25]. Conventional chemotherapy yields a median survival of <3 years [26]. Despite front-line treatment intensification with auto-HCT in eligible cases (including rituximab maintenance), there is still and approximate 50% relapse rate [27–29]. There is no standard approach for R/R MCL, thus representing an unmet need. Bruton tyrosine kinase inhibitors (BTKi) are cornerstone therapy for R/R MCL with three BTKi agents currently FDA approved (ibrutinib, acalabrutinib and zanubrutinib) with significant response rates and durable [30–32]. Yet these agents are not expected to cure MCL, and outcomes of MCL progressing after BTKi are dismal [33].

A phase II study known as ZUMA-2 showed that KTE-X19 or brexucabtagene autoleucel (brexu-cel) induced high response rates (ORR of 93% and CR of 67%), leading to approval in the R/R setting [34].

As CAR T-cell therapy paves the way into a new era of cancer therapeutics, this review provides an in-depth outline of the current status and future directions of CAR T-cell therapy in DLBCL, MCL and other B-cell lymphomas.

Despite the various autologous CAR T products available, the manufacturing process is largely similar. The process starts with the harvesting of T cells through the collection of peripheral mononuclear cells (PMBCs) during leukapheresis. This product is shipped to the facility specialized in manufacture CAR T cells. Depending of the CAR T-cell product there will be a CD3+ T-cell separation followed by expansion and activation. For tisa-cel, activation occurs through anti-CD3 antibodies coated beads, whereas IL-2 is used for T-cell activation for axi-cel. The CAR gen is then inserted into the CD3+ T cells, mainly through a replication-deficient viral vector such as a retrovirus (axi-cel and brexu-cel or lentivirus (tisa-cel). The majority of CAR T cells share the scFv region (which functions as binding domain), FMC63. There are also differences in the costimulatory domain: CD28 (for axi-cel and brexu-cel) and 4–1BB (tisa-cel and lisocabtagene maraleucel) [35].

Diffuse large B-cell lymphoma
Efficacy
ZUMA-1 study was a multicenter trial evaluating axi-cel for R/R DLBCL. It consisted of phases I and II [12,36]. In the phase I, seven patients received low-dose conditioning chemotherapy, followed by axi-cel targeted at 2×10^6 CAR T-cells/kg. Five (71%) patients achieved an ORR within 1 month, including four (57%) of seven achieving a CR with some ongoing remission [36]. In the phase II, 101 patients with refractory DLBCL received axi-cel with resulting ORR (CR) rates of 82% (54%) [12]. These results highlight impressive CR rates vis-à-vis historical controls [11] Table 1.

JULIET was a multicenter global study evaluating tisa-cel in R/R DLBCL, transformed follicular or high-grade B-cell lymphoma. Similar to ZUMA-1, the primary endpoint was ORR and CR rates. In a single-center phase IIA of the trial, 28 patients with B-cell lymphoma received tisa-cel [37]. ORR was 64%, and CR occurred in 43% of 14 DLBCL patients, with 83% remaining in sustained remission. This led to the global phase II pivotal study of the JULIET trial, where 165 patients with R/R DLBCL were enrolled [38]. Among 93 evaluable patients, ORR was 52% (CR = 40%), with durable responses in poor-risk DLBCL Table 1.

Various studies have investigated the safety and efficacy of commercially available CAR T-cell therapies in the nontrial setting so called real-world experience (RWE). A post-marketing study on axi-cel by the Centefr for International Blood and Marrow Transplant Research (CIBMTR), the US CART Consortium (comprising 17 US academic centers) and another retrospective study led by the Dana Farber Cancer Institute with a ORR between 70 and 79% and CR rates around 50%, replicating what it was reported in the ZUMA-1. This efficacy was also seen in patients who would not have been otherwise eligible for the ZUMA-1 clinical trial [39–41]. The CIBMTR registry was also used to report the real-world outcomes of tisa-cel in R/R DLBCL in 70 treated patients with an ORR and CR rates were 59.6 and 38.3%, respectively; that were considered comparable to the JULIET trial [42]. Most recently and outside the USA, reports have emerged from French and UK cohorts [43,44]. The outcomes were quite different in the UK study, with lower response rates; however, prolonged time from patient review/selection to actual CAR T-cell infusion (median time of 63 days) might have contributed to these outcomes. Interestingly the EFS was 39% similar to what was reported in the long-term results of the ZUMA-1 [45]. These results are summarized in Table 1.

Table 1. Anti-CD19 chimeric antigen receptor T-cell therapy in large-cell B-cell lymphoma (selected clinical trials and real-world experience).

Trial/study	ZUMA-1 [43]	JULET [37]	TRANSCEND-NHL001 [42]	Nastoupil et al. [38]	Jacobson et al. [39]	CIBMTR [40]	CIBMTR	Sesques et al. [43]
CAR T product	Axi-cel	Tisa-cel	Liso-cel	Axi-cel	Axi-cel	Axi-cel	Tisa-cel	Axi-cel/Tisa-cel
Patients apheresed (evaluable)	111 (101)	165 (93)	344 (269)	165[†]	65	453 (295)[†]	70 (70)	70 (61)
Bridging therapy (%)	0	90	59	53	40	NA	NA	97%
Median follow-up (months)	27.1	14	18.8	13.8	10.4	6.2	5.8	5.7
ORR (CR) %	83 (58)	52 (40)	73 (53)	82 (64)	70 (50)	70 (52)	60 (38)	63 (48)
Median PFS (months)	5.9	2.9	6.8	8.3	4.5	NA	NA	3.0
12-month PFS	44%	35%	44%	47%	NA	NA	NA	NA
24-month PFS	39%	NA	NA	NA	NA	NA	NA	NA
12-month OS	60%	49%	57.9%	68%	67%	NA	NA	NA
CRS (any grade)	93%	58%	42%	92%	96%	83%	NA	85%
CRS ≥3	11%	22%	2%	7%	17%	14%	4.3%	8%
NT (any grade)	64%	21%	30%	69%	76%	61%	NA	28%
NT ≥3	32%	12%	10%	31%	38%	NA	4.3%	10%

[†] Patients with adequate follow-up.

CAR T: Chimeric antigen receptor T cell; CIBMTR: Center for Blood and Marrow Transplant Research; CR: Complete response; CRS: Cytokine release syndrome; NA: Not available; NT: Neurotoxicity; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival.

Lisocabtagene maraleucel (liso-cel; JCAR017) is a CD19-directed CAR T-cell product incorporating a 4–1BB costimulatory domain and administered in a defined CD4:CD8 of CAR T cells. The multicenter study, TRANSCEND NHL 001, evaluated efficacy of liso-cel in R/R LBCL. The trial included DLBCL NOS, TFL and FL grade 3B. A total of 344 patients underwent leukapheresis, and 269 received liso-cel infusion. Outpatient CAR T-cell infusion was given to 25 patients, with 18 (72%) requiring admission for side effects related to CAR T-cell therapy. With a median follow-up of 18.8 months, the ORR and CR rates were 73 and 53%, respectively. The median PFS and OS were 6.8 and 17.5 months [46] Table 1.

Safety & toxicities

CAR T-cell therapy is associated with known toxicities such as cytokine release syndrome (CRS) and neurologic events (NEs), now termed immune effector cell-associated neurotoxicity syndrome (ICANS) [45,47–49]. CRS consists in a spectrum of signs and symptoms and laboratory abnormalities that are the result of the release and expansion of immune/inflammatory cytokines resulting from CAR T-cell interaction with the targeted antigen. Typical clinical findings are fevers, constitutional symptoms, hemodynamic instability and organ dysfunction, with different degrees of severity [50]. The typical presentation of ICANS consist in toxic encephalopathy with confusion and delirium as the most characteristic symptoms. However, patients can evolve to more serious concerns, such as expressive aphasia, seizures and, rarely, cerebral edema [51,52]. In the phase I portion of ZUMA-1 trial, the primary endpoint was dose-limiting toxicity (DLT). One (14%) of seven patients experienced DLT of grade 4 CRS and neurotoxicity and later died from an intracranial bleed, deemed not related to axi-cel. Grade ≥3 NEs were observed in four (57%) of seven patients. Because all CRS and ICANS events (except for DLT) were self-limiting and reversible, axi-cel was deemed safe for study in a phase II trial [36]. The phase II study of ZUMA-1 also reported all grades and grade ≥3 in 93 and 13%, respectively. For NEs, all grades and grade ≥3 occurred in 65 and 31%, respectively [12]. The 2-year follow-up from ZUMA-1 showed grade ≥3 CRS and NEs occurring in 11 and 32%, respectively [45]. Incidence of all grades CRS and CRS grade ≥3 in the JULIET study were 58% and 22%, respectively. As for NEs, the frequencies of neurologic events of all grades and grade ≥3 were 21% and 12%, respectively [38].

CIBMTR also assessed the safety of axi-cel in real-world practice. CRS (all grades) was observed in 83%, with two deaths attributed to CRS. ICANS (any grade) were reported in 61%, with one death from cerebral edema (of 181 with NEs). Approximately 34% were ≥65 years; however, they had comparable incidences of CRS and ICANS vis-à-vis patients <65 years of age. Toxicities reported by CIBMTR were comparable to ZUMA-1, despite differences in patient characteristics [41]. The multicenter study by Nastoupil et al. also evaluated safety of axi-cel in 163 patients. Grade ≥3 CRS and ICANS were reported in 7 and 31%, respectively [39]. Accordingly, the safety

profile of axi-cel appears comparable to ZUMA-1. Pertaining to tisa-cel, CIBMTR data showed rates of grade ≥3 CRS and ICANS of 4.3 and 4.3%, respectively [42].

In the DLBCL cohort of TRANSCEND NHL-001, all grade CRS and ICANS were observed in 21 (30%) and 14 (20%) patients, respectively, suggesting lower toxicity rates versus axi-cel or tisa-cel, with the caveats of a nonrandomized comparison and use of a different criteria to assess toxicities [53]. In the follow-up update of liso-cel study showed an incidence of CRS and ICANS of 42 and 30%, respectively, with relatively low rates of grade 3–4 CRS (2%) and NT (10%) [46].

Notwithstanding the unique toxicities, namely, CRS and NE, CD19 CAR T cells have revolutionized treatment of R/R DLBCL owing to impressive efficacy and durability of responses. Appropriate strategies and adequate expertise are needed to mitigate toxicities.

The rates of CRS and NE in DLBCL studies are summarized in Table 1.

Mantle cell lymphoma

Earlier studies from the Fred Hutchinson Research Cancer Center (FHRCC) using their anti-CD19 CAR T cells with 1:1 defined CD4:CD8 composition included four MCL patients and showed a modest activity with one of four achieving PR [54]. The follow-up study of the CD28/CD3 anti-CD19 CAR T cell from the NCI included one patient with relapsed MCL that achieved long-term remission [55]. This early experience led to further explore the role of CART in MCL patients in larger studies.

The FULL cohort of the TRANSCEND NHL 001 also included 17 R/R MCL patients [56]. The preliminary efficacy and safety were reported [57]. Patients received liso-cel at two dose levels (DL): DL-1: 50×10^6 (n = 6) and DL-2: 100×10^6 CAR T cells (n = 11) and included five with blastoid/pleomorphic histology, Ki-67 >30% (n = 13), prior ibrutinib failure (n = 16) and prior auto-HCT (n = 6). Any grade CRS occurred in seven patients with CRS ≥3 in one patient (6%). NT occurred in 2 patients (12%) [57,58].

The ZUMA-2 trial is the largest phase II trial in R/R MCL to date, which led to approval of KTE-X19 or brexucabtagene autoleucel. It evaluated KTE-X19 in 74 patients with high-risk MCL [34]. Bridging therapies (37%) were allowed. The intention-to-treat ORR and CR were 85% and 59%, respectively. After a median follow-up of 12.3 months, the 12-month PFS and OS were 61% and 83%, respectively. There were no differences in ORR (CR) rates, PFS and OS among key covariates such as age, MCL histology, TP53 status, Ki67% and BTKi refractoriness. CAR T-cell-related toxicities were CRS (all grades) in 91% (CRS ≥3 in 15%) and NE in 63% (grade ≥3 in 31%). The median onset of CRS and NE were 2 and 7 days, respectively. Tocilizumab and steroids were used in 26% and 38%, respectively. No grade 5 adverse events were reported. KTE-X19 has also been studied in R/R B-cell acute lymphoblastic leukemia [59]. As of August 2020, brexucabtagene autoleucel (KTE-X19) had been approved for the treatment of relapsed/refractory mantle cell lymphoma (Table 2).

Follicular lymphoma

The first reported case of efficacy of CAR T-cell therapy in NHL was in FL [60]. A subsequent National Cancer Institute (NCI) study showed long-term remissions in 2 cases [55]. The initial report of the University of Pennsylvania (UPenn) of CTL019 in refractory B-cell lymphomas included 14 with FL with high-risk features. ORR was 79% (CR = 71%). At a median follow-up of 28.6 months, 70% were disease-free [37]. The FHRCC also reported their experience of anti-CD19 CAR T that included eight patients with refractory FL [61]. With a median follow-up of 24 months, the study showed high and durable response rates, with seven of eight patients achieving CR and all remaining in remission at last follow-up.

ZUMA-5, the first and largest multicenter study to date of anti-19 CAR T-cell therapy (axi-cel) in refractory indolent lymphomas, included 140 patients (FL = 124 and marginal zone lymphoma = 16) enrolled and infused with axi-cel [62]. The efficacy analysis included 80 FL patients with ≥9 months follow-up, and the safety analysis included all axi-cel infused patients. It showed high response rates, with an ORR of 95% (CR = 81%). With a median follow-up on 15.3 months, 80% achieving CR had ongoing responses. The median PFS was 23.5 months. CAR T-related toxicities were: incidence of any grade (grade ≥3 CRS) CRS and any grade NT (grade ≥3 NT) of 77% (7%) and 55% (15%), respectively. Median time of onset of CRS and NT were 4 and 7 days, respectively. The ELARA is a global multicenter study trial evaluating the efficacy of tisagenlecleucel in follicular lymphoma has been presented recently with also encouraging results and tolerable side effects (Table 2).

Table 2. Anti-CD19 chimeric antigen receptor T cell studies in mantle cell lymphoma and follicular lymphoma.						
Trial/study	ZUMA-2 [33]	TRANSCEND-NHL001 [54]	UPenn [36]	FHCRC [58]	ZUMA-5 [59]	ELARA
Disease	MCL	MCL	FL	FL	FL/MZL	FL
CAR T product	KTE-X19	Liso-cel	Tisa-cel	1:1 CD4+/CD8 4–1BB CART	Axi-cel	Tisa-cel
Patients apheresed (evaluable)	74 (68)	25 (17)	16 (14)	8	127 (80)	97 (52)
Median F/U (months)	12.3	8.4	28.6	24	15.3	NA
ORR (CR) %	93 (67)	71 (53)	79 (71)	100 (88)	93 (80)	82.7 (65.4)
Median PFS (months)	NR	5.8	NR	NR	23.5	NR
Median OS (months)	NR	11.1	NR	NR	NR	NR
CRS (any grade) CRS ≥3	91% 15%	41% 6%	57%[†] 18%[†]	59% 0	77% 7%	48.5% 0
Median onset CRS, days (range)	2 (1–13)	7 (2–10)	NA	NA	4 (1–15)	4 (1–14)
NT (any grade) NT ≥3	63% 31%	18% 12%	39%[†] 11%[†]	50% 0	55% 15%	9.3% 1%
Median onset NT, days (range)	7 (1–32)	9 (7–25)	NA	NA	7 (1–177)	8.5 (4–190)

[†]Data of CRS and NT available for the whole group (diffuse large B-cell lymphoma and FL).
CAR T: Chimeric antigen receptor T cell; CR: Complete response; CRS: Cytokine release syndrome; FHCRC: Fred Hutchinson Cancer Research Center; FL: Follicular lymphoma; MCL: Mantle cell lymphoma; MZL: Marginal zone lymphoma; NA: Not available; NR: Not reached; NT: Neurotoxicity; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; UPenn: University of Pennsylvania.

Off the shelf CAR T-cell therapy

Despite the success of autologous anti-CD19 CAR T-cell products, there are limitations. Availability of a CAR T-cell product is affected by manufacturing failure and prolonged manufacturing time [63]. Delays could be challenging in the face of a highly proliferative disease. For instance, in the JULIET study ∼30% of enrolled patients did not receive infusion due to progressive disease, and ∼7% patients had manufacturing failures. In ZUMA-1, 10 patients out of 111 did not receive CART infusion (one patient had manufacturing failure). In ZUMA-2 (MCL), of 74 patients enrolled, six did not receive CART infusion (three due to manufacturing failure, two due to PD). In ZUMA-5, 151 were enrolled and apheresed, 146 received CART infusion (there were no manufacture failures (three ineligible, one death and one with DLBCL transformation) [12,34,38,62]. Additionally, an autologous CAR T-cell product can be affected by T-cell dysfunction related to number of prior therapies, with consequent decrease in functional T cells available for manufacturing. Use of allogeneic CAR T cells ("off-the-shelf" CAR T) is promising to overcome the aforementioned factors. Encouraging activity with donor-derived anti-CD19 CAR T cells were seen in DLBCL, CLL, MCL and ALL without significant increased graft-versus-host disease (GVHD) rates [64,65]. A follow-up report by the NCI of anti-CD19 CAR T cells derived from patients' donors and who relapsed after allo-HCT, included 20 patients with various B-cell malignancies. Eight of 20 achieved either CR or PR with a 6-month PFS of 32%. Nine of 20 had grade ≥3 symptoms of possible CRS. No cases of acute GVHD were reported [65]. Although donor-derived allo-CAR T cells offered promising results, it is not practical due to the need of an HLA-matched donor, thus limited to patients who underwent or are planned for allo-HCT.

Using healthy, nonrelated donors is an alternative source for allogeneic CAR T-cell manufacturing. Strategies to minimize GVHD include T-cell receptor (TCR) gene editing by disrupting the alpha chain of the TCR (TRAC) that is responsible for alloreactivity. A common editing technology is the transcription activator-like effector endonuclease (TALEN). The first allogeneic anti-CD19 CAR T-cell trial using TALEN mediating TRAC editing (UCART19) was reported in B-cell ALL, with promising results and low GVHD rates [66].

At the 2020 ASCO meeting, results of the first in-human trial of anti-CD19 allogeneic CAR T-cell therapy with TALEN-mediated TRAC and CD52 gene editing (ALLO-501) was reported in refractory DLBCL and FL [67]. ALLO-501 was administered with the anti-CD52 antibody at three dose levels. Additionally, ALLO-501 had a safety switch that is activated by rituximab. Patients received lymphodepleting therapy with Flu/Cy. The study enrolled 12 patients (DLBCL = 5) with nine evaluable for efficacy. ORR was 78% with three CRs. The safety profile was manageable, with grade 1–2 CRS in 27% (grade 3 CRS in 5%), 1 developed NT. No patients developed GVHD. Although these results are encouraging, completion of the escalation/expansion phase and longer follow-up are needed.

Areas of unmet needs: post-CAR T-cell relapse management

Unfortunately, 50% or more patients experience relapse [68]. Outcomes post-CAR T-cell relapse are dismal, especially within 3 months post-infusion [69,70]. The mechanisms of relapse or lack of response to CAR T include several factors: product quality, efficacy of conditioning chemotherapy, antigen escape (CD19 loss), increased expression of T-cell exhaustion markers (PD-L1, TIM-3, etc), immunosuppressive tumor microenvironment (increased tumor associated macrophages, myeloid-derived suppressive cells and soluble immunosuppressive factors) [39,71–77]. The US CART consortium reported ORR with checkpoint inhibitors, lenalidomide-based regimens, and chemotherapy of 24%, 20% and 10%, respectively [70]. Radiation therapy seems effective, particularly in localized relapses [78].

Pembrolizumab demonstrated an ORR of 27% (CR = 1; PR = 2) in 12 post-CAR T B-NHL. The authors noted sustained CAR T-cell transgene peaks and expansion in responders [79]. ZUMA-6 investigated combining axi-cel with atezolizumab, a PDL-1 inhibitor, for four doses at different time points (n = 28), showing an ORR of 75% (CR = 46%). Grades ≥3 CRS and NT were similar to ZUMA-1 [80].

Bispecific antibodies (BsAbs) have emerged as an alternative approach to eliminate tumor cells by engaging cytotoxic T cells. Blinatumumab, a CD3/CD19 BsAb, first-in-class agent currently approved for R/R B-cell acute lymphoblastic leukemia [81]. It also showed activity in R/R DLBCL with CR rates of 22–36% (none were post-CAR T-cell relapses) [82,83]. Combination with lenalidomide appears to yield greater activity but longer follow-up is needed to confirm this observation [84]. Limitations are the logistics (continuous infusion administration for 2–4 weeks) and side effects (particularly neurotoxicity). Data on mosunetuzumab (a novel CD3/CD20 BsAbs) from a large study (n = 218) in R/R B-cell NHL (mainly DLBCL and FL) showed an ORR (CR) of 62.7% (43.3%) and 37.1% (19.4%) in FL and DLBCL, respectively [85]. The study included post-CAR T-cell failures (12 patients) with an ORR and CR of 43.5% an 25%, respectively. Similarly, another CD3/CD20 antibody (REGN1979) was evaluated in R/R NHL and included 3 DLBCL cases relapsing after CAR T-cell therapy with two resulting CRs [86]. Epcoritamab (GEN3013) a novel antiCD3/antiCD20 bispecific antibody (DuoBody) administered subcutaneously showed encouraging safety profile and activity in R/R B-cell NHL. This trial reported three objective responses in four post-CAR T-cell DLBCL relapsed cases [87].

Retreatment with CAR T-cell reinfusion was allowed in ZUMA-1 in patients who had initial response and post-biopsy relapse was still CD19 positive. The ORR was 54% with four CR and three PR (out of 13 retreated patients). The median duration of response was 81 days with two still in remission at last follow-up. A larger study and longer follow-up are needed to confirm these results [88].

Dual antigen targeting with CAR T cells is an option aimed at overcoming escape from CD19 loss. The escalation phase of the dual CD19-CD22 lentiviral transduced CAR T cell (41BB/CD3z LV20.19CAR T) was reported in 11 patients with B-cell NHL (DLBCL, MCL and CLL) with an ORR of 82%. There were no reported grade ≥3 CRS or NE [89]. AUTO3 is a CD22–CD19 dual-targeting CAR T cell that uses a retroviral vector and reported preliminary results in a phase I/II study in R/R DLBCL (n = 23) at different doses levels and with/without pembrolizumab. AUTO3 showed remarkably activity with ORR of 65% (CR = 48%) [90].

Discussion

CD19 is an attractive target for immunotherapy, specifically with CAR T cells. Initial success of anti-CD19 CAR T cells in poor-risk DLBCL led to its expansion to other CD19+ malignancies – namely, MCL and FL. Novel strategies are needed for post-CAR T-cell failure.

Combination therapies to improve CAR T-cell efficacy, currently under evaluation, include the addition of targeted, immunomodulatory and/or checkpoint blockade agents – namely utomilumab (4-1BB agonist) + axi-cel (ZUMA-11, NCT03704298), ibrutinib (BTK inhibitor) + tisa-cel (NCT03876028), lenalidomide + axi-cel (ZUMA-14, NCT04002401) and pembrolizumab + tisa-cel (NCT03630159). The PLATFORM trial is a multiarm study that combines liso-cel with an immunomodulatory imide drug (IMiD), PD-L1 inhibitor and BTKi. (NCT03310619; Table 3).

CAR T-cell therapy in the second-line setting may challenge the role of auto-HCT in DLBCL. There are currently three ongoing randomized clinical trials that compare anti-CD19 CAR T-cell versus salvage chemotherapy plus auto-HCT in DLBCL after relapse or lack of response to front-line chemoimmunotherapy: axi-cel (ZUMA-7, NCT03391466), tisa-cel (BELINDA, NCT03570892) and liso-cel (TRANSFORM, NCT03575351). CAR T-cell therapy is also being studied in the frontline setting in the ZUMA-12 trial in high-risk DLBCL (NCT03761056).

Other challenges besides CAR T-cell resistance/relapse include the cumbersome manufacturing process and overcoming T-cell dysfunction. Off-the-shelf or allogeneic CAR T cells are a promising alternative with proven

Table 3. Anti-CD19 chimeric antigen receptor T-cell therapy: combination studies in diffuse large B-cell lymphoma.

CAR T product	Indication	Agents	Phase	NCT N
Axi-cel (ZUMA-6)	R/R DLBCL	Atezolizumab	I/II	NCT02926833
Axi-cel (ZUMA-11)	R/R DLBCL	Utomilumab	I/Ib	NCT03704298
Axi-cel (ZUMA-14)	R/R DLBCL	Lenalidomide and rituximab	I/Ib	NCT04002401
Tisa-cel	R/R DLBCL	Ibrutinib	Ib	NCT03876028
Tisa-cel (PORTIA)	R/R DLBCL	Pembrolizumab	Ib	NCT03630159
Liso-cel (PLATFORM)	R/R DLBCL	CC-122, durvalumab, ibrutinib	I/II	NCT03310619

DLBCL: Diffuse large B-cell lymphoma.

activity and manageable toxicity profile. PBCAR0191 is another anti-CD19 allogeneic product in which the CD19 specific CAR is inserted into the TRAC locus in cells harvested from healthy donors. PBCAR0191 is currently enrolling patients with refractory B-cell NHL, acute lymphoblastic leukemia and chronic lymphocytic leukemia (NCT03666000) [91].

CAR T-cell therapy comes with a hefty price between US$373,000–475,000 for the product only. The price does not account for the cost of the pre-CAR-T workup, hospitalization and treatment of toxicities. The value of CART has been analyzed through cost–effectiveness studies using the quality adjusted life years method has been reported [92]. The impact on budget seems to be as significant as patient access/coverage [93]. Outpatient administration, in-house CAR T-cell manufacturing and improving the safety of the therapy may reduce the overall cost [92].

Conclusion

In conclusion, the role of anti-CD19 CAR T-cell therapy in B-cell NHL shows promise in beyond DLBCL. Evolving strategies such as combinatorial regimens with CAR T and earlier use (second-line setting in DLBCL) may change the treatment paradigm of B-cell NHL.

Future perspective

Current data show the activity and efficacy of anti-CD19 CAR T-cell therapy. It is likely that CD19 will continue to be the most attractive target for B-cell NHL patients. We hope that anti-CD19 CAR T-cell therapy will be approved for follicular lymphoma given the preliminary data of activity shown recently. It is possible that CAR T-cell therapy will be approved as second-line treatment for relapsed DLBCL if the randomized studies (ZUMA-7, BELINDA and TRANSFORM) show positive outcomes in comparison to standard of care.

We also discussed the poor outcomes of post CART relapses, particularly in DLBCL. Efforts in understanding the mechanism and potential strategies are underway, such as combination therapies with targeted agents that may improve the CAR T product (ibrutinib), improve CAR T-cell expansion and trafficking into the tumor (IMiDs and/or checkpoint inhibitors). We also hope that the manufacturing process and logistics will be optimized so that this therapy will be more accessible.

Executive summary

- B-cell non-Hodgkin lymphoma (NHL) is an heterogenous disease and treatable in general; however, a proportion of patients will have refractory disease and options will be limited.
- Targeting CD19 with CAR T-cell therapy is a viable and efficacious strategy to treat poor risk B-cell NHL.
- There are several products available such as axicabtagene ciloleucel, brexucabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel that has shown significant activity in poor risk diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and mantle cell lymphoma.
- Real-life experience data with FDA-approved products have confirmed the efficacy results in DLBCL.
- CAR T-cell therapy will likely move with new indications (i.e., in FL) and possibly in earlier lines (second-line in DLBCL).
- Challenges remain with CAR T-cell therapy in B-cell NHL, such as manufacturing time, access, cost and post-CAR-T relapses. Addressing these challenges may improve the general outcomes with CAR T cell therapy.

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