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CAR-T cell Therapy for Non-Hodgkin Lymphomas: A New Treatment Paradigm

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Abstract

The majority of patients with B-cell non-Hodgkin lymphoma (NHL) can be cured with standard chemoimmunotherapy. However, patients who fail first line therapy have dismal outcomes, particularly if they have disease that is resistant to salvage therapy, including chemoimmunotherapy, radiation and/or autologous stem cell transplantation. Indolent B-NHLs, such as follicular lymphoma (FL), although not generally considered curable may be treated over many years with good prognosis. However, a subset of B-NHLs can undergo histologic transformation into more aggressive subtypes with outcomes similar to aggressive B-NHLs. In recent years, T cells genetically modified with chimeric antigen receptors (CARs), have demonstrated a remarkable capacity to induce complete and durable clinical responses in patients with chemotherapy-refractory lymphomas. Indeed, two autologous CD19-directed CAR-modified T cell products have now been FDA-approved for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL) and transformed FL, while a plethora of other CAR-T cell targets are being explored in ongoing clinical trials. The purpose of this review is to summarize the clinical efficacy and unique toxicities of individually developed CAR-T cell products for the treatment of lymphomas, and their evolution from the laboratory bench to commercialization.

Keywords

cancer; CAR-T cell; chimeric antigen receptor; immunotherapy; lymphoma; oncology

Introduction

Non-Hodgkin lymphomas (NHL), the most common hematologic malignancy, are comprised of a heterogeneous group of lymphoid malignancies derived from both B cell and T cell progenitors or mature T cells, and rarely natural killer (NK) cells. Among the

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Conflict of Interest Statement

HEH is a co-founder of ViraCyte and Marker Therapeutics, has received research support from Cell Medica and Tessa Therapeutics and served on advisory boards for Cytosol, Novartis and Gilead Sciences.

Ethics Statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

heterogeneous NHL subtypes, diffuse large B cell lymphoma (DLBCL) is by far the most common aggressive lymphoma, accounting for 30–35% of all NHLs diagnosed. The majority of patients can be cured with combination chemoimmunotherapy upfront or with salvage high dose chemotherapy and autologous hematopoietic stem cell transplantation (ASCT).¹ However, 15–20% of patients will relapse or develop chemo-refractory disease^{1–4} and these patients have a dismal prognosis, particularly if they are chemo-resistant to salvage therapy or relapse following ASCT.^{5–8} A recent retrospective meta-analysis of patients who achieved stable disease or progressive disease as the best response to chemotherapy, or who relapsed within 12 months of autologous transplant, showed an overall response rate (ORR) of only 26% to salvage therapy and median overall survival (OS) of 6.3 months.⁸ The outcomes for other aggressive NHL subtypes are equally poor after the failure of combination chemotherapy. This study further highlights the unmet need for novel curative therapeutic options for these patients as well as the identification of predictors of response.

The use of adoptive T cell transfer as a therapeutic modality to treat malignant neoplasms has evolved rapidly over the past decade. Genetically modified T cells expressing chimeric antigen receptors (CARs) targeting specific tumor-associated antigens have recently demonstrated impressive potency and durable responses in multiply treatment-refractory B cell malignancies, resulting in the approval of two CD19-specific commercial CAR-T cell products by the U.S. Food and Drug Administration (FDA). Herein, we review the clinical data on CAR-T cells for the treatment of NHL with an emphasis on the efficacy of the various products, challenges of use, ongoing clinical trials, and mechanisms of enhancing the clinical application of these products.

CAR-T design

Chimeric antigen receptors (CAR) are synthetic constructs that combine an extracellular antigen recognition domain derived from a monoclonal antibody specific for a tumor cell surface antigen with an intracellular T cell signaling domain, which results in T cell activation upon antigen binding.^{9,10} The intracellular signaling domain(s) were identified as an extremely important component of the CAR construct after “first generation” CARs, which only integrated a CD3 ζ signaling domain, exhibited limited expansion and persistence despite the ability to respond to antigens and thus short-lived antitumor activity.^{11,12} The introduction of additional co-stimulatory domains such as CD28, 4–1BB, and OX40 in second and third generation constructs led to significantly improved expansion, persistence, and efficacy.^{13–16} While the best co-stimulatory domain is still an area of active investigation, CD28 and 4–1BB have been the most widely used in CAR-T clinical trials with the CD28 CAR construct demonstrating higher peak expansion, and the 4–1BB based constructs showing longer persistence.¹⁷ Which co-stimulatory domain will have the most impact on clinical outcomes remains to be seen.

Clinical outcomes of CD19.CAR T-cells

CD19 is a cell surface protein with expression restricted to both normal and malignant B cells, making it an attractive target for immunotherapy approaches. Many centers have tested the ability of adoptive transfer of CD19.CAR-T cells to eradicate CD19-positive

malignancies. The first report of a clinical response in a patient with NHL using CD19 CAR-T cell therapy was published by Kochenderfer et al., in which they described a patient with multiply-relapsed follicular lymphoma (FL) who achieved a durable partial response after two courses of CAR-T cell therapy in combination with high dose IL-2.¹⁸ The authors later reported that four patients achieved complete remissions (two with DLBCL, NOS and two with primary mediastinal B-cell lymphoma with chemotherapy-refractory DLBCL), of whom three had durable responses.¹⁹ In a larger phase 1 study that included 22 patients, of whom 19 had DLBCL, the NCI group were able to show an ORR of 68% with a complete remission (CR) rate of 47% among patients with DLBCL²⁰ using a CD19-CD28 second generation CAR. The CRs were durable with 11 of 12 ongoing for durations of 7–24 months and 12-month progression-free survival (PFS) of 63% for all participants at the time of study publication. The group also demonstrated that administration of low dose cyclophosphamide plus fludarabine (Cy/Flu) prior to CAR-T cell infusion was adequate to deplete lymphocytes and increase serum levels of IL-15, which positively correlated with peak CAR-T cell expansion and a higher likelihood of obtaining a CR or PR. The toxicity profile in this study was acceptable, as supportive care alone was sufficient to manage the majority of patients who developed cytokine release syndrome (CRS) or neurological symptoms.

Promising results from initial early phase clinical trials lead to licensing studies followed by FDA approval of two commercial CAR-T cell products, tisagenlecleucel (Kymriah; tisa-cel)²¹ and axicabtagene ciloleucel (Yescarta; axi-cel)²², with a third product (lisocabtagene maraceucel; liso-cel) likely to request FDA licensing approval in the near future. Comparing the efficacy between different products directly is difficult given key differences in manufacturing and design of the clinical trials that led to licensure; but overall the clinical outcomes are similar amongst the three products with initial ORR reported between 60–80% and CR rates of 40–60% (Table 1).

The parent construct (formerly known as KTE-C19; now designated axicabtagene ciloleucel) tested in the early NIH trials was ultimately taken to phase I/II multi-center studies for commercial development sponsored by Kite Pharma. Results from the phase II portion of this pivotal clinical trial (ZUMA-1) demonstrated an ORR of 82% with 54% CRs.²³ The time to response ranged from 0.6 to 6 months with a median time of 1 month. Very few relapses were seen in patients who remained in CR at 3–6 months post-infusion with a median duration of response of 11.1 months. Forty percent of patients remained in CR at 1 year and the overall survival (OS) at 18 months was 52%. Of those patients who did not achieve a CR at 1-month post-treatment, 11 of 35 and 12 of 25 patients with a PR and stable disease, respectively, went on to achieve a CR without additional therapies. Two-year follow-up data published in *Lancet Oncology* confirmed prior findings with an ORR of 83% and a CR rate of 58% at a median follow-up of 27.1 months.²⁴ The median duration of response remained 11.1 months and median overall survival was not reached.

Tisagenlecleucel (formerly CTL019), a 4–1BB containing CAR, was developed at the University of Pennsylvania and tested in 28 r/r NHL patients in a case-series study. Sixty four percent of patients had a response, with 43% of patients with DLBCL and 71% of patients with FL (10 of 14) achieving a CR. Eight-six percent and 89% of patients with DLBCL and FL, respectively, maintained a sustained response at a median follow-up of 28.6

months.²⁵ In the phase II multicenter registration trial (JULIET) that led to licensing approval, 40% of 99 patients achieved a CR with 30% remaining in CR at 6 months.²⁶ Four patients (3 FL, 1 DLBCL) with a PR at 3 months achieved a CR by 6 months. The median duration of response and OS was not yet reached at the time of publication, and no patients who achieved a response proceeded to stem cell transplant.

Researchers at the Fred Hutchinson Cancer Research center treated 32 patients with NHL with a 1:1 ratio of CD4:CD8 CD19 CAR-T cells using a 4-1BB costimulatory domain. Their study demonstrated an ORR of 63% with a CR rate of 33% across all lymphoma subtypes.²⁷ Comparable to the ZUMA-1 study, patients who received Cy/Flu prior to infusion had better CAR-T cell expansion and persistence, and a higher CR rate of 50% compared to patients who did not receive fludarabine-containing regimens. Due to two deaths at higher cell doses, subsequent patients were treated with lower doses and still demonstrated responses. Similar findings were noted in the phase I multicenter TRANSCEND NHL study testing JCAR017 (now referred to as liso-cel), which included patients with high risk DLBCL infused with a 1:1 ratio of CD4:CD8 CD19 CAR-T cells.²⁸ In an updated analysis presented at the 2018 ASCO Annual Meeting, the 6-month ORR for this study was 49% with a CR rate of 46% for the pivotal core cohort. Of patients who achieved a CR at 3 months, 88% remained in CR at 6 months, while those who achieved only a PR had a median duration of response of 2.1 months. Liso-cel received FDA breakthrough therapy designation for NHL in December 2016, and a licensing application will likely be submitted in upcoming months if results remain positive. While the aforementioned studies were primarily based in the United States and Europe, several early phase studies conducted in China and recently presented in abstract form have also shown encouraging results.^{29–33}

To date, the efficacy of CAR-T cells has been shown to be independent of classic prognostic markers such as cell of origin (ABC versus GBC), International Prognostic Index (IPI) score, prior number of lines of therapy, or by biologic factors such as intensity of CD19 expression.^{23,26,34} However, peak CAR-T cell expansion has been significantly associated with response and development of neurologic toxicities, with an area under the curve (AUC) 5 times higher observed in responders versus non-responders for axi-cel.²³ Continued long-term follow-up is necessary to determine the curative potential of CAR-T cells, as some patients who initially achieved only partial response (PR) later went on to develop CR as late as 1 year without intervening therapy, suggesting that responses may deepen over time.³⁴ Nevertheless, in patients achieving only PR as the best response, the median duration of response was a dismal 2 months with the axi-cel and liso-cel products.

CAR-T cells for the treatment of T cell lymphomas

Unlike B cell lymphomas, T cell lymphomas are associated with an overall poor prognosis and have limited therapeutic options.^{35,36} Targeting T cell malignancies with CAR-T cells is more challenging due to shared antigen expression between normal, malignant, and therapeutic CAR-T cells, potentially leading to CAR-T cell fratricide (self-killing) and prolonged T cell aplasia.^{37–39} Unlike the manageable B cell aplasia caused by CD19 CAR-T cells, T-cell targeted CAR-Ts may cause profound immunodeficiency similar to that seen

following allogeneic SCT leading to increased risk of severe infections. Furthermore, it can be challenging to harvest an adequate number of normal autologous T cells without contamination by malignant T cells. CD30 is a cell surface molecule overexpressed in peripheral T cell lymphomas (PTCLs), such as anaplastic large cell lymphoma (ALCL), but has limited expression in normal tissues and is only expressed on a subset of T cells. The CD30 antibody-drug conjugate brentuximab vedotin has proven efficacy for the treatment of CD30-positive PTCLs^{40–42} and for these reasons was the first antigen explored for targeting T-cell lymphomas with CARs. In a phase 1 study evaluating the use of CD30-directed CAR-T cells for relapsed/refractory EBV⁺, CD30⁺ lymphoid malignancies, one patient with ALK⁺ systemic ALCL achieved a complete response lasting 9 months.⁴³

CD5 and CD7 have both been identified as potential targets with significant anti-tumor activity seen in preclinical models.^{39,44} There is currently one ongoing phase 1 clinical trial (NCT03081910) investigating the use of CD5 CAR-T cells for treatment of CD5 positive T cell malignancies. The results are eagerly awaited, as there is currently a huge unmet need for the treatment of these diseases for which ASCT is the only potentially curative option for patients who are able to achieve adequate remission to upfront therapies. A phase 1/2 study in China for CD7 positive leukemias and lymphomas utilizing anti-CD7 CAR in NKs cells with TCR ζ , CD28, and 4–1BB signaling domains is actively recruiting but no results are yet available (NCT02742727). A phase 1 anti-CD7 CAR-T trial at our center (NCT03690011) aims to circumvent fratricide of infused T cells by knocking out CD7 by CRISPR-Cas in the T cells expressing the CD7.CAR.⁴⁴ Given the potential for excessive toxicity due to pan-T cell aplasia, the CD5 and CD7 trials are designed as transplant-enabling studies. This strategy should prevent severe complications and provide an opportunity for cure until more data is available on the long-term durability of responses.

An alternative approach to selectively eradicate T cell malignancies is targeting the T cell receptor β -chain constant domains (TRBC1/TRBC2). While normal T cell populations are generally comprised of a mixture of cells expressing either TRCB1 or TRCB2, malignant clonal T cells often exclusively express only one receptor. Maciocia et al. were able to show proof of concept using an anti-TRBC1.CAR that was able to selectively kill both normal and malignant TRBC1 T cells while sparing TRBC2⁺ T cells, which maintained their normal immune function.⁴⁵

Toxicities of CAR-T therapy

One of the most pressing challenges limiting widespread use of CAR-T therapy is the management of toxicities. Cytokine release syndrome (CRS), is a common yet potentially severe and life-threatening adverse event following CAR-T cell treatment, due to the release of massive inflammatory cytokines and markers, such as IL-6, INF γ , TNF α , IL-2, IL-10, GM-CSF, C-reactive protein (CRP) and ferritin, upon activation of CAR-T cells. Timing of symptom onset and symptom severity vary based on the product type and cell dose administered, disease burden, use of lymphodepleting chemotherapy, and the magnitude of immune activation. Symptoms can range from mild to severe, and include fever, fatigue, hypotension, capillary leak syndrome, coagulopathy, and multiorgan dysfunction. Mild cases can be treated with intensive supportive care, but severe cases require treatment with

immunosuppressive therapy. Severe or life-threatening CRS occurs in up to 25% of patients (Table 1).¹⁵ The ZUMA-1 trial for axi-cel reported grade 3 or higher CRS and neurotoxicity events of 13% and 28%, respectively.²³ In the JULIET trial, grade 3/4 CRS occurred in 23% of patients and severe neurotoxicity in only 12%.²⁶ Impressively, the TRANSCEND trial reported the lowest rates of grade 3 or 4 CRS and neurotoxicity at 1% and 14%, respectively.

Tocilizumab, an IL-6 receptor antagonist, has been approved for treatment of severe or life-threatening CRS with one or two doses generally being sufficient to induce rapid reversal and improve symptoms within 7 days.^{27,46–48} Based on current available evidence, tocilizumab does not appear to affect the clinical efficacy of CAR-T cells.^{16,49,50} Patients who do not respond to initial treatment with tocilizumab may be treated with corticosteroids, which has a broader effect on the immune system. Since corticosteroids can induce T cell suppression, their use is reserved for management of severe (grades III and higher) adverse events which can be life threatening.

Given the association of CRS with multiple cytokine elevations, it seems reasonable that these could be used as biomarkers of disease severity or response. However, while elevated cytokine levels have been associated with severe CRS, there are no extensively validated biomarkers predictive of severe CRS and cytokine assays are not widely available. Thus, real-time cytokine analysis is not currently used for clinical decision making in the treatment of CRS. To make cytokine assays more accessible to treating physicians, Faramand et al. presented outcomes on 20 patients with DLBCL treated with axi-cel who underwent a “point of care” cytokine assay designed to predict CRS and/or CRES. They were able to determine a correlation between elevated day 1 levels of IL-6 and angiopoietin 2/angiopoietin 1 ratio with severe CRS. Larger confirmatory studies are underway to apply cytokine testing in CAR-T recipients broadly. A potential surrogate marker that is widely available is serial monitoring of CRP and ferritin levels, which can be obtained real-time to help guide therapy.¹⁶ The overarching goal of CRS management is to maximize therapeutic benefit, while minimizing risk of life-threatening complications. Modifications to lymphodepletion regimens, CAR-T dosing, and management strategies for toxicities are being actively investigated in ongoing studies in an attempt to mitigate the toxicities of CAR-T cell therapy.

Neurotoxicity, also known as CAR-T cell Related Encephalopathy Syndrome (CRES)⁴⁷, and now termed immune effector cell (IEC)—associated neurotoxicity syndrome (ICANS)⁵¹ is considered a separate entity from CRS although they may be associated, and is also a well-recognized adverse event. Patients may develop symptoms at the time of onset of CRS, following resolution of CRS, or in the absence of CRS, although patients who develop severe CRS also tend to exhibit some degree of neurotoxicity. Symptoms may manifest as encephalopathy, aphasia, ataxia, seizures, obtundation, and rarely with potentially fatal cerebral edema or hemorrhage.⁵² The majority of patients who develop neurotoxicity will present within the first 2 weeks following T cell infusion, with spontaneous resolution occurring within 7 to 14 days from onset.⁴⁷ Severe toxicity has been associated with high cell doses and cytokine levels, primarily IL-2, GM-CSF, and ferritin.²³ Tocilizumab has been used to treat neurotoxicity although the benefit is not as striking as that seen with its use in CRS — possibly due to the inability of tocilizumab to cross the blood brain barrier.^{46,53}

Gust and colleagues recently identified central nervous system endothelial activation resulting in disruption of the blood brain barrier as the potential underlying mechanism of neurotoxicity associated with CAR-T cell therapy.⁵³ While further studies are needed to better elucidate the mechanism of action and associated risk factors, their report provides potential for discovery of therapeutics specifically targeting endothelial activation as a means to prevent and/or treat ICANS. The ASBMT (now TCT) recently published a consensus grading scale for CRS and ICANS to provide a more accurate and standardized grading system that can be applied broadly across institutions and CAR-T products; this will allow more prompt recognition and treatment of symptoms and permit easier comparisons across trials.⁵¹

B cell aplasia is an expected “on target off tumor” toxicity of CD19 CAR-T therapy, as CD19 is a pan-B cell marker found on both normal and malignant B cells. However, most patients treated with CAR-T cells have very low levels of circulating B cells and hypogammaglobulinemia due to the heavy pretreatment with anti-CD20 immunotherapy. Long-term persistence of CD19 CAR-T cells may lead to prolonged severe B cell aplasia and increased infectious complications,⁵⁴ but this can be managed with intravenous immunoglobulin (IVIG) supplementation. Recovery of polyclonal B cells has occurred in patients who achieved a response without relapse of lymphoma.^{15,19,20,24,25}

Mechanisms of and potential solutions to overcome immune failure

Explicit comparison of the different trial results is impossible due to the wide variability in CAR-T cell constructs, manufacturing process, underlying disease, patient populations, and clinical trial design. Despite the exciting results seen in current studies, much more research is needed to determine specific CAR, disease, and patient-related factors that will provide the best chance for long-term remissions. One CAR construct may not be adequate when considering the complex nature of the diseases being targeted, and the therapy itself. In order to improve the treatment paradigm and make it more broadly available, several areas must be considered. For instance, selection of more appropriate targets (based on tissue distribution, antibody affinity, etc.) may enhance tumor killing and optimized CAR constructs may increase activation and killing while limiting toxicities. For example a recent report where a CD19 CAR was directed to the T-cell receptor alpha constant (TRAC) locus showed that such edited cells had greater activity than regular CD19 CAR transduced T cells in a murine acute lymphoblastic leukemia model.⁵⁵

Loss of CD19 surface expression is a well described phenomenon of antigen escape in relapses after CD19 CAR-T cell therapy.^{49,56–58} Several early phase clinical trials have shown safety and modest efficacy in targeting other antigens in lymphoma such as CD30,⁴³ kappa light chains,⁵⁹ and CD20.^{12,60–62} raising the possibility of constructing CARs targeting multiple antigen epitopes or administration of multiple CARs (simultaneously or sequentially) with different targets. For lymphoid malignancies, there are currently several trials underway targeting dual antigens with use of combined CARs (Table 2).

Like endogenous T cells, CAR-T cells are also susceptible to immune inhibition via checkpoint blockade present in the tumor microenvironment. Upregulation of PDL-1,

CTLA-4, and LAG3 expression were observed following treatment with axicabtagene ciloleucel (axi-cel), and, more importantly, greater than one-third of patients who failed to respond or relapsed following treatment with axi-cel had high levels of PD-L1 expression on tumor cells.⁶³ Two other studies have also shown increased PD-1 expression on CD19 CAR-T cells following infusion in lymphoma patients.^{19,64} Thus, combining CAR-T cells with immune checkpoint inhibitors might enhance their clinical efficacy.

Preclinical testing of CAR-T and checkpoint inhibitor therapy in murine models has demonstrated augmented activity,^{65,66} and there have also been reports of clinical responses to PD-1 blockade in a small number of patients refractory to CD19 CAR-T cell therapy⁶⁷ leading to multiple clinical trials investigating combination strategies (NCT02706405, NCT03310619, and NCT03287817). Results from ZUMA-6 trial testing axi-cel in combination with atezolizumab for refractory DLBCL showed a reasonable safety profile with a 90% ORR in 9 of 10 evaluable patients (60% CR).⁶⁸ A phase 2 trial is opening soon. Other studies are exploring the use of PD-1 blockade incorporated into CAR-T cells (e.g. anti-PD-1 secreting CAR-T cells; NCT03208556, NCT03298828) based on data from xenograft mouse models showing enhanced antitumor activity and prolonged overall survival.⁶⁹

Allogeneic CAR-T cell therapy

While autologous PBMCs have been the primary source for CAR-T manufacturing, allogeneic (donor-derived) CD19 CAR-T cell generation and infusion for relapse after ASCT also is feasible and safe.^{70–73} All of the studies using donor-derived CAR-T cells demonstrated objective clinical responses without inducing significant graft-versus-host disease (GVHD), suggesting that an “off-the-shelf” CAR T cell bank could be a feasible solution to reduce the time to treatment and cost (Figure 1). Use of gene-editing technologies such as transcription activator-like effector nuclease (TALEN), CRISPR or zinc-finger nucleases to knock out endogenous T cell receptor function has been shown to be a feasible strategy to create off-the-shelf allogeneic CAR-T cell products^{74,75}.

Another approach is to use non-alloreactive allogeneic cells such as virus-specific T cells (VSTs), NK, NK-T, or gamma delta T cells to target tumor-associated proteins.^{76,77} Allogeneic NK cells offer promising potential as an off-the shelf product as they cause minimal GVHD^{78,79} and have a relatively short life span, which could presumably limit the on-target off-tumor effects seen with prolonged persistence of CAR-T cells. Despite the safety and early efficacy seen with use of NK-CARs in phase 1 studies^{77,80–83}, there are some limitations to the use of NK cells. While the short life span maybe beneficial for reducing severe toxicity, poor persistence could negatively impact anti-tumor efficacy. Several studies incorporating cytokine support have shown prolonged NK survival and improved tumor control.^{77,84} Thus, more research is needed to address unanswered questions and better elucidate the clinical efficacy of NK-CAR cells and the potential role they may play in CAR-T therapy.

Conclusions

CAR-T cells have shown great promise in the treatment of relapsed/refractory B cell malignancies, when few other options are available. However, there continues to be room for improvement in the efficacy and safety profile of CAR-T therapy, which will require collaboration from the immunotherapy/cell therapy fields to make this a potentially front-line therapy. Many clinical trials are currently underway in an effort to build upon the successes seen in prior studies. CAR constructs continue to be optimized, and new data is emerging on how to best combine CAR-T cells with other immunotherapies or targeted therapies to further improve efficacy. Additionally, more studies must be performed to determine the optimal timing of CAR-T cell therapy, as current studies have only treated patients with relapsed or refractory disease. Indeed as a next step, both commercially available CAR-T cell products for DLBCL are being tested in comparison with autologous HSCT in upcoming or ongoing phase III clinical trials (BELINDA and ZUMA-7).

Given that very few patients in the ZUMA-1 or JULIET trials proceeded to SCT following CAR-T induced remissions, the jury is still out regarding the question of consolidation with SCT following CAR-T cell induced remissions as the long-term follow-up is still ongoing.

If indeed we are able to achieve the ultimate goal of maximizing “on-target” response while limiting severe “off-tumor” toxicity, CAR-T cells could be paradigm changing and potentially eliminate the need for more toxic therapies such as ASCT, as well as have a significant impact on cost of care. Lastly, the incorporation of genetic, molecular, and response biomarkers may also help better guide future clinical trials and treatment decisions to improve outcomes.

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Figure 1.
Potential Limitations & Benefits of Autologous versus Allogeneic CAR-T cells

Table 1:

Multi-center trials of CD19-CAR T cells for lymphoma

Trial (Name/ID)	DX	N	Construct	LDC	Cell Dose	ORR	CR	DOR	OS	CRS gr3	CRES gr3	Notes
KITE; KTE-C19 (axicabtagene ciloleucel)												
ZUMA-1 ⁵² Phase 1	DLCBL	7	CD3z/ CD28	Flu/Cy	2×10 ⁶ /kg	71%	57%	-	-	14%	57%	3 pts w/ ongoing CR at 12+ mo
ZUMA-1 ²³ Phase 2	DLBCL, tFL, PMBCL	101	CD3z/ CD28	Flu/Cy	2×10 ⁶ /kg	82%	54%	11.1 mo	52% @ 18 mo	13%	28%	40% CR @ 1 yr 3 deaths from SAE
NOVARTIS; CTL019 (tisagenlecleucel)												
JULIET ²⁶ Phase 2	DLCBL	99	CD3z/4- 1BB	Flu/Cy Benda	0.1 – 6×10 ⁸	53%	39.5%	NR	64.5% @ 6 mo	23%	12%	30% CR @ 6 mo
JUNO; JCAR017 (tisocabtagene maraceucel)												
TRANSCEND ⁸⁵ Phase 1	DLBCL; tFL (CORE cohort)	49	CD3z/4- 1BB	Flu/Cy	1×10 ⁸	84%	61%	9.2 mo	88% @ 6 mo	-	-	52% CR @ 6 mo
TRANSCEND ⁸⁵ Phase 1	All DLBCL subtypes (FULL cohort)	68	CD3z/4- 1BB	Flu/Cy	0.5 – 1×10 ⁸	74%	52%	5.0 mo	75% @ 6 mo	1%	14%	Higher 3 mo ORR/CR seen w/ DL2

Benda: bendamustine, CR: complete response, CRES: Cytokine-related Encephalopathy syndrome, CRS: cytokine release syndrome, cy: cyclophosphamide, DL: dose level, DOR: duration of response, Flu: fludarabine, f/u: follow-up, gr3: grade 3, LDC: lymphodepleting chemotherapy, mo: month(s), NR: not reached, ORR: overall response rate, OS: overall survival, PMBCL: primary mediastinal B-cell lymphoma, pts: patients, SAE: severe adverse event, tFL: transformed follicular lymphoma, yr: year.

Table 2.

Ongoing non-CD19 or dual targeted CAR-T Trials for NHL in the US

NCT	Phase	Target	Disease	Location
NCT03081910	1	CD5	R/R lymphoma or leukemia	BCM
NCT03105336	2	CD19	R/R Indolent B-NHL	Multi-center
NCT03019055	1	CD19/20	R/R B-NHL	MCW
NCT03233854	1	CD19/22	R/R B-NHL or ALL	Stanford
NCT03448393	1	CD19/22	R/R B-NHL or ALL	NCI
NCT03330691	1/2	CD19/22	R/R lymphoma	SCH
NCT02153580	1	CD19/EGFR	R/R B-NHL	COH
NCT03277729	1/2	CD20	R/R B-NHL	FHCRC
NCT03244306	1	CD22/EGFR	R/R lymphoma or leukemia	SCH
NCT03049449	1	CD30	R/R lymphoma	NCI
NCT02917083	1	CD30	R/R lymphoma	BCM
NCT02663297	1	CD30	Lymphoma s/p autoSCT	UNC
NCT02690545	1/2	CD30	R/R lymphoma	UNC
NCT03602157	1	CD30/CCR4	R/R lymphoma	UNC

ALL: acute lymphoblastic leukemia; BCM: Baylor College of Medicine; B-NHL: B-cell non-Hodgkin lymphoma; COH: City of Hope; FHCRC: Fred Hutchinson Cancer Research Center; MCW: Medical College of Wisconsin; NCI: National Cancer Institute; SCH: Seattle Children's Hospital; UNC: University of North Carolina.