Efficacy and Safety of Innovative Experimental Chimeric Antigen Receptor (CAR) T-cells versus Axicabtagene ciloleucel (Yescarta) for the Treatment of Relapsed/Refractory Large B-Cell Lymphoma (LBCL): Matching Adjusted Indirect Comparisons (MAICs) and Systematic Review

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ABSTRACT

Despite favorable results of CAR T-cell therapy for relapsed/refractory large B-cell lymphoma (R/R LBCL), several challenges remain, including incomplete response, immune-mediated toxicity, and antigen-loss relapse. We delineated the relative clinical benefit of the novel approaches compared to the currently approved CAR T-cell therapies. In the absence of head-to-head comparisons and randomized controlled trials, we performed Matching Adjusted Indirect Comparisons to quantify the relative efficacy and safety of experimental CARs against Axicabtagene ciloleucel (Yescarta), the first FDA-approved CAR. A total of 182 R/R LBCL patients from 15 clinical trials with individual patient data (IPD) were pooled into eight populations by their CAR T-cell constructs and +/- ASCT status. The study endpoints were Progression-Free Survival (PFS), grade ≥ 3 cytokine release syndrome (CRS), and grade ≥ 3 neurotoxicity (NT). Tandem CD19.CD20.4-1BBζ CARs indicated favorable efficacy and safety, whereas the co-infusion of CD19 & CD20 with 4-1BBζ showed no clinical benefit compared to Yescarta. Third generation CD19. CD28. 4-1BBζ, and sequential administration of autologous stem cell transplantation (ASCT) and CD19. CARs presented statistically insignificant yet improved PFS and safety except for ASCT combined intervention which had suggestively higher NT risk than Yescarta. CARs with modified co-stimulatory domains to reduce toxicity (Hu19. CD8.28Zζ and CD19. BBz.86ζ) presented remarkable safety with no severe adverse events; however, both presented worse PFS than Yescarta. Third-generation CARs demonstrated statistically significantly lower NT than Yescarta. CD20. 4-1BBζ data suggested targeting CD20 antigen alone lacks clinical or safety benefit compared to Yescarta. Further comparisons with other FDA-approved CARs are needed.

Keywords: Chimeric Antigen Receptor (CAR), Diffuse Large B Cell Lymphoma (DLBCL), Lymphoma, Comparative Effectiveness Study, Matching Adjusted Indirect Comparison, Systematic Literature Review, Axicabtagene ciloleucel (Yescarta)

INTRODUCTION

Large B-cell lymphomas (LBCL) comprise diverse types of B-cell Non-Hodgkin Lymphoma (NHL), of which diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype, accounting for approximately a quarter of NHL cases worldwide (1). Survival rates have greatly improved over the past decades, particularly in the immunochemotherapy era, with a 5-year relative survival rate reported between 55.4% and 62.0% in developed countries (2). However, despite the advances achieved with rituximab-based regimens, up to 50% of patients with advanced-stage de novo DLBCL, for instance, will

eventually relapse, even after achieving a complete response (CR) (3). If progression occurs during the initial treatment phase or soon after a brief CR, only 30% to 40% will respond to salvage chemotherapy and will be able to undergo consolidation with autologous stem cell transplantation (ASCT) (4). Even so, among these patients, roughly half will ultimately relapse after transplantation (5). The prognosis, in such cases, is poor, especially for those who have high-risk factors or relapse within 12 months post-ASCT (4,5). Thus, effective treatment for R/R LBCL remains a highly unmet need.

To date, only three CAR T-cell products, axicabtagene ciloleucel (Axi-cel, Yescarta), tisagenlecleucel (Tisa-cel, Kymriah), and lisocabtagene maraleucel (Liso-cel, Breyanzi), are approved by the Food and Drug Administration (FDA) for R/R LBCL (6–8). Despite the unprecedently high efficacy of these CAR T-cell

therapies compared to historical outcomes for patients with R/R LBCL, current challenges, such as incomplete response, immune-mediated toxicity, and post-treatment relapse, remain. For example, in the ZUMA-1 trial for R/R LBCL, only 39% of patients maintained a CR to the therapy at the median of 27-month follow-up despite the initially high (82%) objective response rate (ORR) achieved (7,9). In an attempt to optimize CAR T-cell characteristics to address these inadequacies, preclinical researches identified tumor antigen escape and CD19 antigen downregulation as potential causal factors for the suboptimal response and relapse observed after CAR T-cell therapy (10). Tumor antigen escape leads to low antigen density via transfer of target antigens from the tumor cells to the CAR T-cells. This process, known as trogocytosis, has been observed with CD19, CD22, mesothelin, and B-cell maturation antigen (BCMA) (11).

Existing evidence prior to this study encompasses diverse strategies focused on advancing CAR T-cell performance. Specific approaches already notable for both their feasibility and clinical and safety benefit include (i) Multi-antigen targeting CAR T-cells obtained through co-infusion or sequential administration of single-targeted CAR T-cells against different antigens; alternatively, tandem and bicistronic constructs expressing two different CARs on a single or on separate chimeric proteins, respectively (12); (ii) Third and advanced generation CAR T-cells using integrated co-stimulatory domains (13–15); (iii) Enhanced co-stimulatory domains intended to reduce toxicity and preserve potency (16,17); (iv) Combination therapy of CAR T-cells and immune checkpoint inhibitors (18); (v) Co-administration of ASCT and CAR T-cells (19–21); (vi) Alternative antigen targeting (other than CD19), such as CD20, CD22, CD27, ICOS, and OX40 (22).

Summary of the evidence prior to this study
Dual targeting CAR T-cells: Preclinical studies demonstrated high anti-tumor potency with tandem CD19/CD20 CAR T-cells (23,24), sequential infusion of CD19 and CD79b CARs (25), co-infusion of CD19 and CD38 CAR T-cells (26), and CD19/CD37 constructs (27). The clinical benefit of tandem CD19/CD20 CARs (28–30), co-infusion of CD19 and CD20 CARs (31), and mixed infusions of CD22 and CD19 CAR T-cells (32,33) has been evaluated in small early phase clinical trials with demonstrated feasibility and varying levels of efficacy and safety.

Among the next-generation CAR T-cells, more mature data exist for the third-generation CAR T-cells incorporating both CD28ζ and 4-1BBζ co-stimulatory signaling domains. In mice models, third-generation CAR T-cells demonstrated improved T-cell persistence and stronger anti-tumor potency compared to second-generation constructs (34). In addition, the clinical benefits of third-generation CARs in LBCL patients were evaluated in early phase trials (13–15). However, whether the addition of 4-1BBζ co-stimulatory domains to a common CD28ζ domain enhances such clinical benefits compared to second-generation CAR T-cells in this population is still unclear.

Variations of CAR T-cells with modified co-stimulatory domains aimed at reducing treatment-related toxicity include (1) Hu19.CD8.28Z, containing a fully human single-chain variable fragment (scFv), CD8α-based hinge and transmembrane domains (16); (2) CD19. BBz.86, with an 86-amino-acid fragment from human CD8α sequence comprising the hinge and transmembrane domains (17). Both CD19. BBz.86 and Hu19. CD8.28Z CAR T-cells demonstrated exceptional safety, yet attenuated efficacy, based on the CR rates of 29% and 39% observed, respectively, compared to the 54% CR rate noted among the LBCL patients receiving Axi-cel (Yescarta).

ASCT and CAR T-cell therapy: Multi-center randomized clinical trials are underway to determine the comparative efficacy and safety of CAR T-cell therapy alone vs. ASCT combined with systemic therapies for the treatment of R/R LBCL (refer to Discussion section for additional details). The study comparing locally manufactured CD19. CD28ζ CAR T-cells in China to ASCT alone (NCT03196830) demonstrated superior efficacy and safety of the CAR T-cell product compared to ASCT in R/R NHL patients (35). Whether the sequential administration of ASCT and CAR T-cells holds higher clinical benefits than CAR T-cells alone remains to be elucidated. Of note, this has already been shown to be feasible and safe in three clinical trials (19–21). These clinical trials evaluated the safety and efficacy of the sequential administration of ASCT and CD19. CD28ζ CAR T-cell therapy in LBCL patients (19–21), the investigators hypothesized that this combination would reduce cytokine production while exerting a high anti-tumor potency by increasing the expansion and persistence of CAR T-cells.

CD20. 4-1BBζ CAR-T cells demonstrated high anti-tumor activity against LBCL in preclinical studies (36), and few clinical trials tested second-generation CD20 CAR T-cells in this disease (36–38). Clinical trials evaluating third-generation CD20 CARs are currently underway in China (NCT02710149), in the USA (NCT03277729) – evaluating MB-106, a fully human third-generation CD20.4-1BBζ.CD28 ζ CAR T-cell construct –, and in Germany (NCT03664635), with MB-CART20.1 CARs (39,40). Targeting CD20 was shown to be exceptionally more efficacious in follicular lymphoma, as demonstrated with the success of rituximab, an anti-CD20 monoclonal antibody, which led to the current rituximab-based first-line combination treatment for most NHL types (41). The fact that 30–40% of LBCL patients relapse after rituximab suggests that targeting CD20 alone is not enough (41). This has set the basis for comparative insights between CD20 and CD19-targeted CAR T-cells, thereby shedding light on the development of the dual targeting approaches mentioned above.

As summarized above, key preclinical and clinical data became available regarding the innovative approaches aimed to extend the durability of response beyond the achievements of the currently approved CAR T-cells. Yet, up to date, no direct comparative efficacy and safety study exists to shed light on the

relative advantages of the experimental CAR T-cell products versus currently approved CAR T-cell therapies.

The aim of this study is to indirectly compare the efficacy and safety of the currently available experimental CAR T-cell products to Yescarta, the first FDA-approved CAR T-cell therapy (thereby harboring the longest follow-up data available to date) to provide guiding insights into the ongoing efforts to advance CAR T-cell therapy for the treatment of R/R. LBCL.

METHODS
Matching-adjusted indirect comparison (MAIC)
To overcome the fact that all currently available CAR T-cell trials are single-arm studies and that individual patient-level data (IPD) are only available for experimental CAR T-cell products and not for the ZUMA-1 trial (the comparator), we used unanchored matching-adjusted indirect comparison (MAIC) as a primary method (42). MAIC techniques can attenuate bias when comparing multiple treatments assessed in different studies by matching patient-level data from single-arm clinical trials to aggregate data from comparator trials. Additionally, MAIC provides a more robust adjustment for cross-trial differences in patient characteristics than traditional meta-regressions, given the higher accuracy obtained from IPD than from aggregate data (43).

Data sources
For Yescarta, published aggregate data was used from the ZUMA-1 trial (disease- and baseline characteristics data), evaluating the efficacy of Yescarta for the treatment of LBCL patients (7). For experimental CAR T-cell products as comparator arms, IPD was available from the corresponding peer-reviewed publications identified through a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline-based systematic review. This study included the clinical trials of patients who received CAR T-cell therapies for the treatment of R/R LBCL after two or more systemic therapies regardless of the type of CAR T-cells, geography, health care setting (inpatient and outpatient), and demographic characteristics (age, gender, race, and ethnicity). Clinical trials that provided concomitant therapies together with CAR T-cell products (except for bridging or lymphodepleting chemotherapy) were excluded. We searched the extensive scope of electronic databases, including PubMed, Cochrane Central, Medline via Ovid, Embase via Ovid, Scopus Elsevier, Web of Science, and Education Resources Center (ERIC). Conference proceedings were identified from the American Society of Hematology (ASH), American Society of Clinical Oncology (ASCO), and European Hematology Association (EHA) websites. North American and international trials were ascertained through a search in ClinicalTrials.gov, International Standard Randomized Controlled Trial Number (ISRCTN) registry, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), Deutsches Register Klinischer Studien (DRKS), Chinese Clinical Trial Registry (ChiCTR), European Clinical Trials Register

(www.clinicaltrialsregister.eu), Latin American and Caribbean Health Science Information Database (LILACS), and Australian and New Zealand Clinical Trials Registry. We searched for unpublished trials and the grey literature using Google, Grey Literature Report (greylit.org), and OpenGrey (opengrey.eu) to identify potential publication bias. To reduce potential confounding to the study results due to the difference in study designs, we conducted a feasibility assessment and Risk of Bias Assessment using an NIH Quality Assessment Tool for Case Series Studies (44) by comparing the eligible studies in terms of their PICOS (population, intervention, comparator, outcomes, and study design) and the NIH recommended criteria. Consequently, we excluded four studies with significantly different PICOS from the rest of the studies (Figures S1). Details regarding the literature search terms and queries, study selection, data extraction, and the risk of bias assessment can be found in the published protocol for the present study (45).

We created eight independent interventions of distinct types of CAR T-cell products. Five of them were based on pooled populations from multiple trials evaluating similar CAR T-cell constructs, as shown in Table 1 and listed below:

1. Dual targeting using tandem CD19. CD20 with 4-1BB, a pool of two trials;
2. Dual targeting by co-infusion of CD19 & CD20 with 4-1BB;
3. Third-generation CARs: CD19 with CD28 & 4-1BB, a pool of three trials;
4. Modified co-stimulatory domain for reduced toxicity: Hu19.CD8.28Z;
5. Modified co-stimulatory domain for reduced toxicity: CD19.BBz.86;
6. Sequential administration of ASCT and CD19.CD28ζ, a pool of three trials;
7. Alternative target-antigen: CD20. 4-1BBζ CARs, a pool of two trials;
8. Alternative co-stimulatory domain: CD19. 4-1BBζ CARs in Chinese patients, a pool of two trials.

Where possible, pooling patients has enabled an increase in statistical power and hypothesis testing by CAR T-cell types. Additionally, we excluded the trials with fewer than 10 patients (Figure S1). The trials of CAR T-cells that eventually evolved into Yescarta and the early phase trials of those developed into Kymriah and Breyanzi, currently FDA-approved products, were also excluded from this study.

Reconstructed patient-level progression-free survival (PFS) data for the ZUMA-1 trial: for the calculation of the hazard ratio (HR) and its 95% confidence interval (CI) associated with the PFS of each pooled CAR T-cell population versus Yescarta, we reconstructed individual patient PFS data from the ZUMA-1 trial through a validated algorithm developed by Guyot and colleagues (2012) (46). This was achieved by obtaining the number of patients at risk and the total number of events along

Table 1. Summary of Clinical Trials, Pooled Populations by CAR T-cell structure, and Study Endpoints.

Intervention strategies	Pooled populations	Target Antigens	Signaling domains	Clinical Trial Registry Numbers	Disease Histology	N received infusion	Study Endpoints	Trial Centers	References
Dual targeting	Tandem CD19. CD20 with 4-1BB	Tandem CD19.CD20	4-1BB	NCT03019055	DLBCL, trDLBCL,RS	14	ORR, PFS, OS, CRS, NT	Medical College of Wisconsin, WI, USA	Shah2020 [30]
				NCT03097770	DLBCL, trDLBCL	19	ORR, PFS, OS, CRS, NT	PLA General Hospital, Beijing, China	Tong2020 [29]
	Co-infusion CD19 & CD20 with 4-1BB	Co-infusion of CD19 & CD20	4-1BB	NCT03207178	DLBCL, trDLBCL	21	ORR, PFS,OS,CRS, NT	Xuzhou Medical University, China	Sang2020 [31]
Third generation	CD19 with CD28 & 4-1BB	CD19	CD28-41BB	NCT01853631	DLBCL, trDLBCL	13	ORR, PFS, CRS, NT	Baylor College of Medicine, TX, USA	Ramos2018 [15]
				NCT02132624	DLBCL, trDLBCL	4	ORR, OS, PFS, CRS, NT	Uppsala University Hospital, Sweden	Enblad2018 [13]
				NCT03121625	DLBCL	9	ORR, OS, PFS, CRS, NT	Hebei Medical University, China	Huang2020 [14]
Modified constructs for reduced toxicity	Hu19.CD8.28Z	CD19	Human-CD28	NCT02659943	DLBCL, trDLBCL	19	ORR, EFS, CRS, NT	NCI, MD, USA	Brudno2020 [16]
	CD19. BBz.86	CD19	4-1BBz.86	NCT02842138	DLBCL, trDLBCL	21	ORR, DOR, CRS, NT	Peking University, Cancer Institute, China	Ying2019 [17]
ASCT+ CAR T-cell	Sequential ASCT and CD19. CD28	CD19	CD28	NCT01497184	DLBCL, trDLBCL	7	ORR, PFS, CRS, NT	MD Anderson Cancer Center, TX, USA	Kebriaei2016 [19]
				NCT01840566	DLBCL, trDLBCL,RS	13	ORR, PFS, CRS, NT	Memorial Sloan Kettering Cancer Center, NY, USA	Sauter2019 [20]
				NCT01318317	DLBCL	4	ORR, PFS, OS, CRS, NT	NCI, City of Hope Cancer Center, CA, USA	WangX2016 [21]
Alternative target antigen	CD20. 4-1BB	CD20	4-1BB	NCT01735604	DLBCL	6	ORR, PFS, CRS, NT	PLA General Hospital, Beijing, China	WangY2014 [36]
				NCT01735604	DLBCL	8	ORR, PFS, CRS, NT	PLA General Hospital, Beijing, China	Zhang2016 [38]
Alternative co-stimulatory domain	CD19. 4-1BB	CD19	4-1BB	NCT03156101	DLBCL, HGBCL	10	ORR, PFS, CRS, NT	Zhengzhou University, Zhengzhou, China	Chen2020 [48]
				ChiCTR15007668	DLBCL	14	ORR, PFS, OS, CRS, NT	Second Military Medical University, Shanghai, China	WangT2020 [49]

ASCT - autologous stem cell transplantation; CAR - chimeric antigen receptor; CD - cluster of differentiation;
ChiCTR - Chinese clinical trial registry; CRR - complete response rate; CRS - cytokine release syndrome;
DLBCL - diffuse large B-cell lymphoma; DOR – duration of response; HGBCL – high-grade B-cell lymphoma; Hu - human;
NCT - national clinical trial; NT - neurotoxicity; ORR - objective response rate; OS – Overall survival; PFS - progression-free survival;
EFS – event-free survival, NCI – National Cancer Institute; RS - Richter's transformation to DLBCL; trDLBCL – transformed DLBCL.

with the geometric coordinates of the published PFS Kaplan-Meier (KM) curve associated with Yescarta over a 24-month follow-up time using Origin® digitizing software.

Outcomes assessed
We selected PFS (the time from treatment initiation till disease progression or death, whichever occurs first) for efficacy and grade ≥ 3 cytokine release syndrome (CRS) and neurotoxicity (NT) for safety outcomes, given that the purpose of the study was to determine the relative benefit of experimental CAR T-cell products compared to Yescarta in terms of response durability and severe toxicity. Table 1 presents the study endpoints reported by the eligible studies. Given all 15 eligible trials had complete PFS data in this study, the follow-up length of studies had no impact on the PFS, the study outcome. Overall survival (OS) was not used since multiple studies had not reached the median follow-up time at the time of this analysis. We did not focus on the objective response rate or the initial response types since these measures do not reflect the response durability and also the presence of notable cross-trial variation in the timing of the objective response measurements.

Statistical methods
Given the existing evidence limited to single-arm trials, we conducted unanchored MAICs to adjust for cross-trial heterogeneity in baseline characteristics. Matching covariates were selected following the National Institute for Health and Care Excellence (NICE) Guidelines (42) given: a) mutually reported disease- and patient baseline characteristics, where the feasibility assessment revealed cross-trial heterogeneity and b) whose clinical meaningfulness was confirmed by clinicians and experts (Table 2).

In MAIC, patients in experimental CAR T-cell trials with IPD were re-weighted to match the mean baseline characteristics in the ZUMA-1 trial. The weights were estimated by the method of moments applied to the IPD to ensure that the summary statistics of the baseline characteristics of the IPD become similar to those of the aggregate data (43). Based on the calculated weights, individual patient-level PFS and percentage of grade ≥3 CRS and NT were re-weighted for further survival and logistic regression analyses. For the comparator arm, we used the reconstructed individual patient level PFS for Yescarta (see Materials section). Given these data, the Cox proportional hazards (PH) model estimated the HR and 95% CI for PFS associated with each pair of eight pooled CAR T-cell populations versus Yescarta. Corresponding weighted KM curves were fitted. Finally, logistic regression models were used to compute the odds ratio (OR) and 95% CI based on the re-weighted data for both safety outcomes: grade ≥ 3 CRS and NT.

A recent MAIC study of Yescarta vs. Kymriah identified LBCL-specific key prognostic covariates. This study demonstrated refractory status and number of prior therapies as the most influential variables on the CAR T-cell treatment outcomes (47). We identified the mutually reported key baseline covariates and used categorizations as follows: age (<58 years), disease stage (<3), histology (diffuse LBCL/other types), refractory status, number of prior lines of therapy (>4), and extranodal disease status. The pack of mutually reported covariates varied for each pair of distinct pooled CAR T-cell population and Yescarta, as this was dictated by the size of the IPD pooled population and the mutual availability of the data in both the IPD and ZUMA-1 trials, as shown in Table 2. The effective sample size (ESS) is the pseudo-population generated by weighing the comparative trial population (42). All analyses were performed using R version 4.1.0 (2021).

RESULTS
Individual Patient Data (IPD): Through a systematic review, we identified 15 clinical trials for experimental CAR T-cell products (Table 1) with IPD, as presented in the PRISMA flow diagram in Figure S1, Supplementary Materials.

Table 2 presents the ESS and weighted versus unweighted summary statistics values of the matching baseline covariates across each pooled CAR T-cell population versus ZUMA-1.

***Dual targeting CARs versus Yescarta** Tandem CD19. CD20 with 4-1BB:* The current MAIC analysis has shown that the tandem CD19.CD20.4-1BBζ CAR T-cells presented suggestive evidence of increased PFS (HR = 0.58; 95% CI, 0.33-1.01), reduced grade ≥ 3 CRS (OR=0.70; 95% CI: 0.18-2.76), and a statistically significantly lower odds of grade ≥ 3 NT (OR=0.14; 95% CI: 0.02-0.78) compared to Yescarta (Table 2 & 3).

Co-infusion CD19 & CD20 with 4-1BB
In contrast, co-infusion of CD19 and CD20 CAR-T cells had a numerically worse PFS (HR=1.33, 95% CI: 0.70-2.54) than Yescarta. However, this finding was not statistically significant. IPD for safety outcomes was not available from this study, however, a naïve direct comparison shows that this co-infusion approach presented higher grade ≥ 3 CRS (28.5% vs. 13% in ZUMA-1) and lower NT (9.5% vs. 28% in ZUMA-1) than Yescarta.

Third-generation CARs versus Yescarta
Suggestive evidence of improved PFS was found, with HR=0.85 (95% CI: 0.43-1.66), and safety in terms of grade ≥3 CRS, with OR=0.20 (95% CI: 0.02-2.12), and NT, with OR=0.20 (95% CI: 0.04-0.94), associated with third-generation CAR T-cells versus Yescarta.

Modified co-stimulatory domains for reduced toxicity
Both Hu19.CD8.28Z and CD19. BBz.86 CAR T-cells presented excellent safety profiles, with no grade ≥3 CRS and NT events reported. In contrast, both of these CAR T-cells presented a worse PFS: Hu19.CD8.28Z, with HR=2.00 (95% CI: 1.01-3.96), and CD19. BBz.86, with HR=1.67 (95% CI: 0.90-3.09), compared to Yescarta, though with no statistical significance for the latter.

Table 2. Key Baseline Characteristics and MAICs of Experimental CAR T-cells versus Yescarta regarding Progression-Free Survival ⱡ

Intervention strategies	Pooled populations	Mutually reported variables	ZUMA-1 (%,median age)	Post - / Pre - weighting (%,median age)	N patients, pooled population	ESS	PFS, HR (95CI%)	References
Dual targeting	1) Tandem CD19. CD20 with 4-1BB	DLBCL Prior chemo ≥3 CD19 status CD4 & CD8 ratio Relapse after ASCT	0.76 0.70 0.90 0.48 0.21	0.76 / 0.86 0.70 / 0.82 0.90 / 0.86 0.48 / 0.46 0.21 / 0.16	33	25	0.58 (0.33-1.01)	Shah2020 [30] Tong2020 [29]
	2) Co-infusion CD19 & CD20 with 4-1BB	Age, median Prior chemo ≥3 Disease Stage I or II	58 0.70 0.15	58 / 55 0.70 / 0.57 0.15 / 0.14	21	15	1.33 (0.70-2.54)	Sang2020 [31]
Third generation	3) CD19 with CD28 & 4-1BB	Age, median DLBCL Refractory Prior chemo ≥3	58 0.76 0.78 0.70	58 / 62 0.76 / 0.69 0.78 / 0.77 0.70 / 0.69	26	23	0.85 (0.43-1.66)	Ramos2018 [15] Enblad2018 [13] Huang2020 [14]
Modified constructs for reduced toxicity	4) Hu19.CD8.28Z	DLBCL Refractory Prior chemo ≥3 Relapse after ASCT	0.76 0.78 0.70 0.21	0.76 / 0.74 0.78 / 0.63 0.70 / 0.63 0.21 / 0.26	19	17	*2.00 (1.01-3.96)	Brudno2020 [16]
	5) CD19. BBz.86	Age, median Refractory Prior chemo ≥3 DLBCL	58 0.78 0.70 0.76	58 / 48 0.78 / 0.71 0.70 / 0.71 0.76 / 0.76	21	20	1.67 (0.90-3.09)	Ying2019 [17]
ASCT+ CAR T-cell	6) Sequential ASCT and CD19. CD28	Age, median DLBCL Refractory Relapse after ASCT	58 0.76 0.78 0.21	58 / 58 0.76 / 0.77 0.78 / 0.38 0.21 / 0.42	24	13	0.73 (0.30-1.74)	Kebriaei2016 [19] Sauter2019 [20] WangX2016 [21]
Alternative target antigen	7) CD20. 4-1BB	Age, median Prior chemo ≥3 Disease Stage I or II	58 0.70 0.15	58 / 61 0.643 0.286	14	13	1.04 (0.52-2.06)	WangY2014 [36] Zhang2016 [38]
Alternative co-stimulatory domain	8) CD19. 4-1BB	Age, median Male Extranodal disease	58 0.68 0.70	58 / 43 0.68 / 0.63 0.70 / 0.50	24	11	0.47(0.18-1.28)	Chen2020 [48] WangT2020 [49]

ⱡ Hazard ratio (HR) and 95% CI (confidence interval) based on Cox proportional hazards models.

ASCT - autologous stem cell transplantation; CAR - chimeric antigen receptor; CI - confidence interval; CD - cluster of differentiation; ESS - effective sample size; HR - hazard ratio; Hu - human; MAIC - matching adjusted indirect comparison; PFS - progression-free survival; *statistical significance at α=0.05; ZUMA-1 – name of Yescarta clinical trial.

Sequential administration of ASCT and CD19. CD28ζ versus Yescarta

Our findings have shown a seemingly favorable PFS (HR=0.73; 95% CI: 0.30-1.74) and reduced grade ≥ 3 CRS (OR=0.25; 95% CI: 0.02-3.68), but increased NT (OR=1.78; 95% CI: 0.60-5.28) for the sequential administration of CD19. CD28ζ CAR T-cells within 2 to 6 days after ASCT compared to Yescarta. None of these findings was statistically significant.

Alternative target antigen: CD20. 4-1BBζ versus Yescarta

No notable clinical benefit or harm was found in this pooled population treated with CD20. 4-1BBζ versus Yescarta in terms of PFS (HR= 1.04; 95% CI: 0.52-2.06) and CRS (OR=1.04; 95% CI: 0.20-5.38). NT could not be assessed in this case due to a lack of IPD data availability.

Alternative co-stimulatory domain: CD19. 4-1BBζ in Chinese patients versus Yescarta

The MAIC of CD19. 4-1BBζ CARs based on the pooled population of two small trials conducted in China, Shanghai (48,49), versus Yescarta showed no significant difference but suggestively better PFS than Yescarta, with HR=0.47 (95% CI: 0.18-1.28) and slightly reduced grade ≥ 3 CRS (OR=0.95; 95% CI: 0.15-5.94) than Yescarta. NT could not be examined since the corresponding data was not provided in the trials.

DISCUSSION

Dual targeting strategies versus Yescarta

We had two strategies (Tandem vs. co-infusion) of dual targeting (CD19, CD20) CARs. The tandem CAR T-cells demonstrated improved PFS compared to Yescarta. In contrast to the tandem therapy, co-infusion of CD19 and CD20 CAR T-cells had reduced PFS than Yescarta. This finding corroborates preclinical studies that demonstrated the higher efficacy and safety of tandem CAR T-cells than that of co-infusions (10). The reduced survival benefit and increased CRS associated with the co-infusion of different CAR T-cell targets may be associated with: (1) additive toxicity from stronger cytokine storm through the amplified number of targetable antigens; (2) competitive targeting limiting the expansion of other CAR T-cells; (3) compromised engraftment due to the interference of multiple antigens (12,50,51). A literature review on the multi-antigen targeting strategies showed more data for CD19 and CD22 covering various administration approaches (sequential and co-infusion) and different constructs (tandem and bicistronic). Sequential administration of CD19 and CD22 CAR T-cells in 12 DLBCL patients (32) and co-infusion in 36 NHL patients (33) resulted in objective response rates of 77% and 83% and in grade ≥3 CRS rates of 14% and 21%, respectively. Tandem CD19 and CD22 CAR T-cells appeared feasible and potentially efficacious in R/R B-cell acute lymphoblastic leukemia (B-ALL) (52). Although these preliminary results are somewhat comparable to the 82% ORR and 13% grade ≥3 CRS observed in ZUMA-1, longer follow-up data are required to assess whether sequential and mixed infusion approaches reduce post-CAR T-cell therapy relapse. Bicistronic CD19. CD22 trials in pediatric

and adult R/R B-ALL (53,54) demonstrated unprecedently high CR rates (100%) and a notable safety profile, with a single occurrence of grade ≥3 CAR T-cell related encephalopathy syndrome (CRES) in the pediatric trial. As for B-cell lymphoma, bicistronic CD19.CD22 trials led by Shah and colleagues (NCT03448393), Miklos and colleagues (NCT03233854), and Pulsipher and colleagues (NCT03330691) are currently ongoing.

Third-generation CARs versus Yescarta

Although the results associated with the third-generation CAR T-cells versus Yescarta were not statistically significant, the slight protective effects observed could be due to multifunctional cytokine secretion and improved persistence of T-cells from the concurrent expression of CD28ζ and 4-1BBζ co-stimulatory domains versus expression of the CD28ζ co-domain alone (55). In addition, *in-vivo* studies demonstrated that adding 4-1BBζ to the second-generation construct protects CD28ζ tumor-specific cells from activation-induced cell death while supporting central memory cells and mitochondrial functions (56). In alignment with this existing evidence, three contributing IPD trials of the pooled population in our study reported high expansion and improved persistence of T-cells in common. Moreover, all three trials of third-generation CAR T-cells analyzed in this study highlighted that the patients with less tumor burden and prior responders to chemotherapy had higher tumor clearance benefits than patients with more tumor burden and non-responders to chemotherapy (13–15).

Modified co-stimulatory domains for reduced toxicity

Hu19.CD8.28Z and CD19. BBz.86 CAR T-cells were designed to exert minimal toxicity while preserving anti-tumor potency as compared to Yescarta. Reduced cytokine-mediated toxicity is often accomplished by attenuating CAR signal strength and enhancing T-cell persistence (16,17,57). Consequently, this enables tumor immune escape and hampers the anti-tumor potency of CAR T-cells, particularly for low antigen density tumors (58). This phenomenon may explain our findings of lower toxicity and reduced PFS benefit of two anti-CD19 CAR T-cells, Hu19.CD8.28Z and CD19. BBz.86.

Multiple preclinical studies are underway toward determining the CAR structure that might achieve minimum toxicity and maximum efficacy for low antigen density tumors. A recent in-vivo leukemia model demonstrated the high potency of a new CD19. CD28ZH/T-4-1BBζ construct, despite the low antigen density of the leukemic cells, while accomplishing a similar efficacy to Yescarta (58). Further studies are required to assess how these preclinical findings translate into clinical benefits for lymphoma patients.

Sequential administration of ASCT + CD19. CD28ζ versus Yescarta

Providing ASCT prior to CAR T-cell administration is believed to reduce tumor burden, diminish immunosuppressive microenvironment, and boost lymphodepletion, thereby reducing the number of regulatory T-cells and myeloid cells.

Table 3. MAICs of Experimental CAR T-cells versus Yescarta Regarding Grade ≥3 CRS and NT

Intervention strategy	Pooled populations	N received infusion	Sum of weights	Number of CRS, grade ≥ 3	OR (95%CI) CRS, grade ≥ 3	Number of NT, grade ≥ 3	OR (95%CI) NT, grade ≥ 3	References
Dual targeting	1) Tandem CD19. CD20. 4-1BB	33	28	3	0.70 (0.18-2.76)	2	*0.14 (0.02-0.78)	Shah2020 [30] Tong2020 [29]
	2) Co-infusion CD19 & CD20 with 4-1BB	21	NA	NA	NA	NA	NA	Sang2020 [31]
Third generation	3) CD19 with CD28 & 4-1BB	26	26	1	0.20 (0.02-2.12)	1	*0.20 (0.04-0.94)	Ramos2018 [15] Enblad2018 [13] Huang2020 [14]
Modified constructs for reduced toxicity	4) Hu19. CD8.28Z	14	20	0	0	0	0	Brudno2020 [16]
	5) CD19. BBz.86	21	20	0	0	0	0	Ying2019 [17]
ASCT+ CAR T-cell	6) Sequential ASCT and CD19. CD28	24	16	3	0.25 (0.02-3.68)	7	1.78 (0.60-5.28)	Kebriaei2016 [19] Sauter2019 [20] WangX2016 [21]
Alternative target antigen	7) CD20. 4-1BB	14	13	2	1.04 (0.20-5.38)	NA	NA	WangY2014 [36] Zhang2016 [38]
Alternative co-stimulatory domain	8) CD19. 4-1BB	24	12	4	0.95 (0.15-5.94)	NA	NA	Chen2020 [48] WangT2020 [49]

ASCT - autologous stem cell transplantation; CAR - chimeric antigen receptor; CI - confidence interval; CD - cluster of differentiation; CRS - cytokine release syndrome; OR - odds ratio; Hu - human; MAIC - matching adjusted indirect comparison; *statistical significance at α=0.05; NT - neurotoxicity; ZUMA-1 – name of Yescarta clinical trial.

Nevertheless, our findings on ASCT + CD19. CD28ζ versus Yescarta were inconclusive, as none of the findings were statistically significant. The direction of the results remained unchanged in separate analyses for the U.S. and Chinese trials. Nevertheless, the feasibility and clinical benefit of the concurrent administration of ASCT with CAR T-cell therapy may not be justifiable since this combined regimen would not be available to about half of the patients who are transplant-ineligible due to chemo-refractory disease and to half of those who received ASCT still at risk for disease relapse post-autografting (59). Of note, combining ASCT with CAR T-cell therapy may not be necessary if CAR T-cell therapy alone is superior to ASCT, as previously shown (35). Intensive efforts are underway to understand whether CAR T-cell therapy is efficacious and safe to replace ASCT in earlier lines of treatment of LBCL. A few randomized multi-center clinical trials are underway comparing the FDA-approved CAR T-cells - Yescarta in the ZUMA-7 trial (NCT03391466), Kymriah in the BELINDA study (NCT03570892), and Breyanzi in the TRANSFORM trial (NCT03575351) - versus the standard of care comprised of systemic therapies followed by ASCT.

Alternative target-antigen: CD20. 4-1BBζ versus Yescarta

CD19 has been a primary target in CAR T-cell therapy for LBCL due to its pan B-cell expression and increased expression in B-cell leukemias and lymphomas (60). In contrast, CD20 and CD22 have limited expression in mature B cells. Nevertheless, targeting both CD19 and CD20 has an additive effect, given CD20 antigen's higher average density of surface molecules per tumor cell, combined with CD19's pan B-cell lineage cell expression, with extended-expression in certain CD20-negative tumor subsets (61). Since all patients in this trial were treated with rituximab before CD20.4-1BBζ CAR T-cell administration, the question of whether CD20 CAR T-cells would be more efficacious among rituximab-näive patients remains to be clarified.

Alternative co-stimulatory domain: CD19. 4-1BBζ in Chinese patients versus Yescarta

This CAR T-cell product has an identical construct to that of tisagenlecleucel (Kymriah), but the trial was conducted in a different study population in China. Despite the lack of statistical significance of the findings for the CD19. 4-1BBζ CAR T-cells in Chinese patients in this study compared to Yescarta, the slight numerical improvement seen in safety associated with the CD19. 4-1BBζ CAR T-cells is consistent with the recent MAIC of Kymriah and Breyanzi to Yescarta (47, 63). 4-1BBζ is one of the well-established co-stimulatory domains incorporated into the CD19 CARs in Kymriah and Breyanzi, while Yescarta contains a CD28ζ co-domain. The impact of the CD28ζ versus 4-1BBζ co-stimulatory domains on CAR T-cell behavior has been studied in in vivo and multiple clinical studies in B-ALL. CD19. CD28ζ CAR T-cells show a faster and higher peak expansion, yet reduced T-cell persistence compared to 4-1BBζ-containing CARs (62). Nonetheless, it is not fully clear whether

CAR T-cell persistence is a strong determinant of response durability in LBCL as it is for B-ALL.

Comparative effectiveness studies on currently approved CAR T-cell therapies

A recently published MAIC of Yescarta versus Kymriah demonstrated superior efficacy of Yescarta, with higher CR rates (RR=1.62, 95% CI: 1.16-2.27) and improved OS (HR=0.51, 95% CI: 0.31-0.83), yet increased toxicity, with grade 1-2 CRS, with OR = 6.20 (95% CI: 2.76-13.93), and grade ≥ 3 NT, with OR=2.20 (95% CI: 0.98-3.60) in R/R LBCL (47). Another recently published MAIC of Yescarta versus Breyanzi demonstrated similar efficacy, while slightly favoring Yescarta (PFS with HR=1.30; 95% CI, 0.96-1.77). However, Breyanzi presented a significantly safer profile than Yescarta (grade ≥3 CRS and NT with OR= 0.16; 95% CI, 0.06-0.47, and OR=0.31, 95% CI, 0.18-0.54, respectively) (63). Thus, among the currently approved CAR T-cells, based on the existing MAICs, Yescarta appears to present higher efficacy than Kymriah and comparable efficacy to Breyanzi. In contrast, the latter two incorporating 4-1BBζ co-domains demonstrate a safer profile regarding CRS and NT than Yescarta. The lower toxicity and similar efficacy observed with Breyanzi versus Yescarta relates to its ability to induce a low variability in cytokine production (such as IL-2, IFN-γ, TNF-α). This was accomplished through controlled manufacturing to maintain the ratio of CD4+ and CD8+ to 1:1 under optimized culture conditions. In vivo studies are underway to clarify the exact underlying mechanisms in this regard (64).

Strengths, Limitations, and Future Study

To the best of our knowledge, this study is the first to report the indirect comparison of experimental CAR T-cells to Yescarta, the first FDA-approved CAR T-cell product. In addition, this study incorporated a systematic literature review with a MAICs, a statistical tool to indirectly compare safety and efficacy of treatments in the absence of direct head-to-head comparisons and the presence of single-arm trials. The results of this study need to be evaluated in light of certain important limitations.

To reduce the potential confounding due to the differences in PICOS (population, intervention, comparator, outcomes, and study design) among the studies identified through our systematic review, we conducted a feasibility assessment prior to running the analyses and excluded four studies with substantially different PICOS. Even though we attempted to account for cross-trial heterogeneity, it is important to acknowledge the residual case-mix and beyond case-mix heterogeneity (65). This implies that the study results are subject to residual confounding, since MAICs can only correct for cross-trial heterogeneity in mutually reported disease- and patient baseline characteristics. Inevitable differences between the eligible clinical trials in trial management strategies, study designs, protocols, presence or absence of conditioning regimens and/or bridging therapies, CAR T-cell engineering techniques, and manufacturing processes potentially introduce bias in indirect comparison study results. For example, ZUMA-1

did not use bridging therapy, as opposed to some of the eligible IPD trials in this study that used bridging therapy. It is unclear as to how this may have affected our results since the role of bridging chemotherapy in the CAR T-cell setting is not fully understood and is subject to multiple confounding factors.

Furthermore, methodological limitation stems from the fact that the MAIC method assumes all key prognostic factors differentially distributed across studies are taken into account (42,65). However, we were unable to adjust all important prognostic factors since eligible studies reported different patient characteristics to describe their study samples, which limited the number of common key baseline covariates reported by experimental CAR T-cell trials in relation to ZUMA-1. For example, two important key baseline covariates for R/R DLBCL which were lacking in experimental CAR T-cell trials were International Prognostic Index (IPI) and Eastern Cooperative Oncology Group (ECOG) Performance Status. Furthermore, even when a similar patient characteristic was reported across studies, it was often measured by different scales in different papers, which renders the adjustment by MAIC impossible, including IPI, age-adjusted IPI, and Revised-IPI measurements. A deeper inconsistency found across the trials was the differential definition of relapsed disease as a baseline characteristic between ZUMA-1 and eligible IPD trials in this study. ZUMA-1 defined refractoriness as patients who had stable disease (SD) as their best response to the last line of therapy or those who had relapsed within 12 months of a consolidative ASCT. In IPD trials, besides using the same definition as that of the ZUMA-1 trial, progression at any time after the last line of therapy was also included as a criterion for relapsed disease. Therefore, we categorized patients as either refractory or relapsed in the MAICs irrespective of the type of relapse. Regarding the MAIC of safety outcomes, IPD trials used different grading systems for CRS and NT from ZUMA-1, which used the Lee criteria (66).

Hence, only a few important and mutually reported variables were adjusted for in the analysis. Consequently, any underlying difference in other unmeasured patient characteristics across studies could undermine the validity of these findings. For example, pooled populations for the dual targeting and third-generation CAR T-cells comprised ethnically diverse patients pooled from the clinical trials conducted in China and the USA (Table 1). However, to the best of our knowledge, there is no data available yet on whether ethnicity impacts CAR T-cell treatment outcomes. Apart from simple inverse weighting, advanced statistical methods based on doubly robust estimation have been developed to adjust for between-trial heterogeneity in patient characteristics (65). These approaches require specifying one model for the weight and another model for the outcome of interest. The advantage is that only one of these two models needs to be correctly specified to obtain valid and less biased results. Hence, this study aims to build a basis for further exploration but not to draw definitive conclusions, given the small sample sizes of the included trials. Although a larger case series is needed to confirm these results, our findings are biologically plausible and clinically meaningful when corroborating them with the existing preclinical and clinical literature in the field.

CONCLUSION

In conclusion, our MAIC results suggest a dual targeting approach using tandem CD19.CD20.4-1BB may have enhanced efficacy and safety compared to Yescarta. The hazard ratios of PFS were numerically in favor of the third-generation constructs, the sequential administration of ASCT and CD19.CD28 CAR T-cells, and the CD19. 4-1BBζ manufactured and evaluated among Chinese patients, even though none of them was statistically significant. The safety-enhanced CAR T-cell constructs included in our analysis, such as Hu19. CD8.28Z and CD19. BBz.86, demonstrated a remarkable safety profile, with no severe adverse events reported, yet without improvement in PFS compared to Yescarta.

While our results have shown the potential efficacy and safety advantages of tandem dual targeting approaches over Yescarta, multi-targeted CAR T-cells, in general, are unlikely to overcome the other resistance mechanisms beyond target antigen loss, such as the resistance involved with IL-6/STAT3 pathways, disruption of gene regulations for T-cell differentiation and exhaustion (67), and PD-L1 induced inhibition of CAR-T cells (68). Given the experimental CAR T-cells addressed in this study are still in their early stage of development, it is premature to discuss the clinical implications in a real-world setting. Nevertheless, our study is a groundbreaking work that serves as a basis for further exploration of novel CAR T-cell products designed to overcome the limitations of currently approved CAR T-cell therapies. The future research is to extend this study results with longer follow-up data to identify the comparative efficacy, safety, and feasibility of novel CAR T-cell products to the currently approved CARs, including Yescarta, Kymriah, and the most recently approved lisocabtagene maraleucel (Breyanzi).

Data Availability: Individual patient data obtained from the eligible clinical trials analyzed in this study and any materials generated during the study are available and will be released via a material transfer agreement and study protocol, if available.

Ethical and informed consent statement: This study was based on the published data by the eligible clinical trials in this study. Therefore, ethics committee approval or informed consent statement were not required since the study did not involve patients or the public in the design, conduct, reporting, or dissemination plans.

Abbreviations

ASCT - autologous stem cell transplantation; B-ALL - B-cell acute lymphoblastic leukemia; BCMA - B-cell maturation antigen; CAR - chimeric antigen receptor; CD - cluster of differentiation; ChiCTR - Chinese clinical trial registry; CI - confidence interval; CR - complete response; CRES - car T cell-related encephalopathy syndrome; CRR - complete response rate; CRS - cytokine release syndrome; CRS - cytokine release syndrome; DLBCL - diffuse large B-cell lymphoma; DOR - duration of response; EFS - event-free survival; ESS - effective sample size; HGBCL - high-grade B-cell lymphoma; HR - hazard ratio; Hu - human; IFN-γ - interferon-γ; IL-2 - interleukins-2; IPD - individual patient data; KM - Kaplan-Meier; LBCL - large B-cell lymphoma; MAIC - matching adjusted indirect comparisons; NCT - national clinical trial; NHL - non-Hodgkin lymphoma; NT - neurotoxicity; OR - odds ratio; ORR - objective response rate; OS - overall survival; PFS - progression free survival; PH - proportional hazards; PPCR - principles and practice of clinical research; PRISMA - preferred reporting items for systematic reviews and meta-analyses; R/R LBCL - relapsed/refractory large B-cell lymphoma; RR - relative risk; RS - Richter's transformation; scFv - single-chain variable fragment; SD - stable disease; TNF-α - tumor necrosis factor-α; trDLBCL - transformed DLBCL; ZUMA-1 - name of Yescarta clinical trial.

NOVELTY AND IMPACT

Although currently approved CAR T-cells demonstrated unprecedently high response in relapsed / refractory LBCL in the salvage setting, lack of outcome durability and toxicity remain. We delineated the relative clinical benefit of the innovative experimental CAR T-cell approaches to Yescarta for insights into the ongoing efforts to address these inadequacies. Tandem CAR T-cells may provide higher efficacy and safer profile than Yescarta. Toxicity attenuated CAR T-cells present remarkable safety but no Progression-Free Survival (PFS) benefit.

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