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Review Paper

Chimeric Antigen Receptor T-Cell Therapy in B-Cell Lymphoma and Leukemia: A Narrative Review of Efficacy, Toxicity, Resistance, and Access Across the Approved CD19-Directed Products

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ABSTRACT

CD19-directed chimeric antigen receptor (CAR) T-cell therapy has transformed the treatment landscape for relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) and B-cell non-Hodgkin lymphomas, with five CD19-directed products now approved based on pivotal single-arm and randomized trials. This narrative literature review synthesizes the current evidence on efficacy, toxicity, mechanisms of resistance, real-world performance, and access barriers, drawing on approximately 50 primary sources published predominantly between 2017 and 2026, including pivotal trials, long-term follow-up studies, randomized comparative trials, mechanistic and resistance studies, toxicity-management guidance, real-world evidence, and health-system access literature. Across diffuse large B-cell lymphoma (DLBCL), five-year follow-up of ZUMA-1 demonstrated a durable 43% overall survival with axicabtagene ciloleucel, while second-line randomized trials established CAR T-cell therapy as superior to autologous transplantation for early relapsed or refractory disease, with a four-year overall survival of 54.6% versus 46.0% in ZUMA-7. In Peadiatric and young adult B-ALL, five-year follow-up of ELIANA showed 63% overall survival with tisagenlecleucel, while adult B-ALL outcomes with brexucabtagene autoleucel demonstrated a 60% complete remission rate and 25.4-month median overall survival. Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome remain the principal acute toxicities, managed with ASTCT consensus grading, tocilizumab, and corticosteroids. Antigen escape, particularly CD19 loss, remains the dominant mechanism of relapse, with dual-antigen CD19/CD22 and allogeneic CAR constructs under investigation. Real-world registry data generally validate trial-level efficacy and safety, although meaningful differences exist between

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approved products. High costs, frequently exceeding $370,000–475,000 per infusion, and manufacturing/logistical barriers remain major obstacles to equitable global access. Overall, CD19-directed CAR T-cell therapy has established curative potential in a meaningful subset of patients, while antigen escape and access inequity remain principal unresolved challenges

INTRODUCTION

Chimeric antigen receptor (CAR) T-cell therapy represents one of the most significant therapeutic advances in hematologic oncology of the past decade. By genetically engineering a patient's own T lymphocytes to express a synthetic receptor that combines an extracellular antigen-recognition domain, typically a single-chain variable fragment (scFv) derived from a monoclonal antibody, with intracellular T-cell activation and costimulatory signaling domains, CAR T-cell therapy redirects cytotoxic T-cell activity toward a tumor-associated surface antigen in a manner that is independent of major histocompatibility complex presentation [1,2]. The first-in-class approval of tisagenlecleucel in 2017, nearly three decades after the initial conception of the chimeric antigen receptor, marked the beginning of a rapidly expanding field that now encompasses five FDA-approved CD19-directed products for B-cell malignancies and additional approved constructs targeting B-cell maturation antigen (BCMA) in multiple myeloma [1,3].

CD19 has proven to be a particularly favorable CAR-T target in B-cell malignancies: it is expressed across nearly the entire B-cell lineage, from early pro-B cells through mature, antigen-experienced B cells, but is absent from hematopoietic stem cells and non-B-cell tissues, allowing for tumor cytotoxicity with a predictable and manageable on-target, off-tumor toxicity profile (B-cell aplasia and hypogammaglobulinemia) [1]. Building on this target, five anti-CD19 CAR T-cell products have received regulatory approval for relapsed or refractory B-cell malignancies: tisagenlecleucel (Kymriah), axicabtagene ciloleucel (Yescarta), lisocabtagene maraleucel (Breyanzi), brexucabtagene autoleucel (Tecartus), and, most recently, obecabtagene autoleucel — spanning indications across diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and B-cell acute lymphoblastic leukemia (B-ALL) [5,8].

Despite this transformative efficacy, CAR T-cell therapy is associated with unique and potentially life-threatening acute toxicities, principally cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which necessitated the co-development of standardized grading systems and management algorithms as the field matured [41,44]. In parallel, a substantial proportion of patients who initially respond to CD19 CAR T-cell therapy ultimately relapse, most commonly due to antigen escape mechanisms that render the malignant clone invisible to the infused CAR construct [49,51,54]. Access to CAR T-cell therapy also remains highly unequal, constrained by manufacturing complexity, treatment-center capacity, and list prices commonly exceeding $370,000–475,000 per infusion, which places this therapy beyond reach for many patients both within high-income health systems and, more acutely, in low- and middle-income countries [58,60,64].

This narrative review synthesizes the current evidence base on CD19-directed CAR T-cell therapy across the principal B-cell lymphoma and leukemia subtypes for which it is approved, organized around five domains: (1) the pivotal efficacy data supporting each approved product and indication; (2) the pathophysiology, grading, and management of CRS and ICANS; (3) mechanisms of resistance and relapse, with a focus on antigen escape; (4) real-world evidence validating or refining trial-derived expectations; and (5) the access, cost, and manufacturing

barriers that continue to limit the reach of this therapy, together with the next-generation approaches under active development to address them.

1.1 Review Objectives

- To summarize pivotal and long-term follow-up efficacy data for CD19-directed CAR T-cell therapy in diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, and B-cell acute lymphoblastic leukemia.
- To describe the pathophysiology, standardized grading, and current management approach for cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.
- To characterize the principal mechanisms of resistance to CD19 CAR T-cell therapy, with emphasis on antigen escape and its relationship to CAR construct design.
- To synthesize real-world evidence on the effectiveness and safety of approved products outside the clinical trial setting.
- To outline the cost, manufacturing, and global access barriers to CAR T-cell therapy and the emerging strategies intended to address them.

2. MATERIALS AND METHODS

2.1 Literature Search Strategy

A narrative literature review was conducted using PubMed/MEDLINE, Blood, Blood Advances, Journal of Clinical Oncology, The Lancet (and Lancet Oncology), New England Journal of Medicine, Nature Medicine, Frontiers in Immunology, and Cancer Cell International, supplemented by conference proceedings from the American Society of Hematology (ASH) annual meeting, the American Society of Clinical Oncology (ASCO) annual meeting, and the European Society for Medical Oncology (ESMO) congress, together with registry sources from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the European Society for Blood and Marrow Transplantation (EBMT). Search terms included combinations of "CAR T-cell therapy," "chimeric antigen receptor," "CD19," "diffuse large B-cell lymphoma," "follicular lymphoma," "mantle cell lymphoma," "acute lymphoblastic leukemia," "cytokine release syndrome," "ICANS," "antigen escape," "tisagenlecleucel," "axicabtagene ciloleucel," "lisocabtagene maraleucel," "brexucabtagene autoleucel," "real-world evidence," and "access barriers."

2.2 Source Selection

This review prioritized pivotal registrational trials and their long-term follow-up analyses (ZUMA-1, JULIET, TRANSCEND NHL 001, ZUMA-7, TRANSFORM, ELARA, ZUMA-2, ZUMA-3, ELIANA), randomized phase 3 comparative trials, systematic reviews and meta-analyses, ASTCT consensus guidance documents, large multicenter registry analyses (CIBMTR, national CAR-T registries), and recent (2024–2026) mechanistic and next-generation therapy literature. Approximately 50 primary sources meeting these criteria were identified and are synthesized in the sections that follow; full citation details are provided in the reference list.

2.3 Scope and Limitations of the Review

This is a narrative rather than a systematic review: source selection, while broad and drawing on high-impact, peer-reviewed and registry literature, was not governed by a pre-registered protocol, a fixed set of database-specific Boolean search strings, or formal PRISMA-style screening and dual-extraction, and no formal quality-scoring or risk-of-bias assessment was applied to included studies. Cross-trial comparisons of efficacy and toxicity (e.g., between axicabtagene ciloleucel and tisagenlecleucel) draw substantially on matching-

adjusted indirect comparisons (MAIC) and retrospective real-world cohorts rather than head-to-head randomized trials, which do not exist for most product-to-product comparisons in this field; such indirect comparisons are subject to residual confounding despite statistical adjustment. The review focuses specifically on CD19-directed autologous CAR T-cell therapy in B-cell lymphoma and B-ALL and does not comprehensively cover BCMA-directed therapy in multiple myeloma, CAR-T in T-cell malignancies, or CAR-T in solid tumors, except where relevant to illustrate broader mechanistic or next-generation concepts.

3. RESULTS: SYNTHESIS OF THE EVIDENCE

3.1 CAR Construct Design and Mechanism of Action

All five approved CD19-directed CAR T-cell products share a common structural framework: an extracellular CD19-targeting scFv (most commonly derived from the FMC63 murine antibody clone), a hinge and transmembrane domain, one of two costimulatory domains (CD28 or 4-1BB [CD137]), and an intracellular CD3-zeta signaling domain that triggers T-cell activation upon antigen engagement [13,50]. The choice of costimulatory domain has proven to be a clinically consequential design decision: axicabtagene ciloleucel and brexucabtagene autoleucel incorporate a CD28 costimulatory domain, associated with more rapid but shorter-lived CAR T-cell expansion and generally higher rates of severe CRS and neurotoxicity, whereas tisagenlecleucel and lisocabtagene maraleucel incorporate a 4-1BB costimulatory domain, associated with more gradual expansion, greater persistence, and a comparatively lower incidence of severe acute toxicity [46,50].

Manufacturing begins with leukapheresis to collect the patient's peripheral blood T cells, which are then activated, genetically transduced (typically via retroviral or lentiviral vector) to express the CAR construct, expanded ex vivo, and reinfused into the patient following lymphodepleting chemotherapy, most commonly fludarabine and cyclophosphamide, which conditions the host immune environment to support CAR T-cell engraftment and expansion [12,13]. This manufacturing process typically requires several weeks, during which many patients with rapidly progressive disease require bridging therapy to maintain disease control [8].

3.2 Efficacy in Diffuse Large B-Cell Lymphoma

DLBCL, the most common non-Hodgkin lymphoma subtype, was the first indication for which CD19 CAR T-cell therapy demonstrated pivotal efficacy in the relapsed/refractory, heavily pretreated setting. In the registrational ZUMA-1 trial, axicabtagene ciloleucel produced an objective response rate of 82–83% and a complete response rate of 58% among patients with refractory large B-cell lymphoma; five-year follow-up demonstrated sustained overall survival with a 5-year OS rate of approximately 43% and disease-specific survival of 51%, with no new safety signals emerging over extended follow-up and polyclonal B-cell recovery observed in 91% of evaluable patients by three years, providing among the strongest evidence to date for the curative potential of this therapy in a subset of patients [9,11,12,14].

The JULIET trial established tisagenlecleucel in a comparable population, with five-year follow-up demonstrating an objective response rate of 53.0% (39.1% complete response) and an estimated 60-month overall survival probability of 32% among all infused patients, rising to 56% among those achieving a complete or partial response [16,19,23]. The TRANSCEND NHL 001 trial established

lisocabtagene maraleucel in this same third-line-or-later setting; matching-adjusted indirect comparisons across these three third-line pivotal trials have suggested broadly comparable long-term survival outcomes between tisagenlecleucel and lisocabtagene maraleucel after population adjustment, with liso-cel showing numerically favorable point estimates for response and a more favorable toxicity profile in some analyses, though the absence of head-to-head randomized data limits the strength of any product-superiority conclusion [15,18,22].

The field's most consequential recent development has been the demonstration that CAR T-cell therapy is superior to standard second-line therapy — high-dose chemotherapy followed by autologous stem-cell transplantation — for patients with early relapsed or primary refractory large B-cell lymphoma. In the randomized phase 3 ZUMA-7 trial, second-line axicabtagene ciloleucel produced a 27.4% relative reduction in mortality compared with standard of care, with a 4-year overall survival of 54.6% versus 46.0%, despite 57% of standard-of-care patients receiving subsequent cellular immunotherapy off-protocol after progression; median event-free survival favored axi-cel substantially (hazard ratio 0.398) [25,27,29,31]. The TRANSFORM trial demonstrated a similar second-line benefit with lisocabtagene maraleucel, and together these two randomized trials have repositioned CD19 CAR T-cell therapy from a last-resort, heavily pretreated-population therapy to a standard second-line option for appropriate patients with high-risk relapsed/refractory large B-cell lymphoma [16,26].

The longest available follow-up data in this space, a 10-year outcomes analysis of tisagenlecleucel (as CTL019) in 38 patients with relapsed/refractory B-cell non-Hodgkin lymphoma (24 with large B-cell lymphoma, 14 with follicular lymphoma), reported a median follow-up of 10.1 years with no relapses occurring beyond 5.4 years and a 10-year lymphoma-free survival of 32%, offering direct evidence that durable remission with CD19 CAR T-cell therapy can represent a genuinely curative outcome in a meaningful subset of patients [6].

3.3 Efficacy in Follicular Lymphoma and Mantle Cell Lymphoma

In relapsed/refractory follicular lymphoma, an indolent but generally incurable B-cell lymphoma, the ELARA trial established tisagenlecleucel with durable response rates that were sustained on long-term follow-up regardless of the number of prior lines of therapy; a comparable indolent-lymphoma population treated with axicabtagene ciloleucel in the ZUMA-5 trial demonstrated efficacy at three-year follow-up that was broadly consistent with ELARA, despite ZUMA-5 patients having received fewer prior lines of therapy on average [68,70,74].

In mantle cell lymphoma, a B-cell lymphoma subtype characterized by generally poor outcomes after Bruton tyrosine kinase inhibitor (BTKi) failure, brexucabtagene autoleucel demonstrated an objective response rate of 93% and complete response rate of 67% in the pivotal ZUMA-2 cohort 1 trial among BTKi-pretreated patients; five-year follow-up confirmed durable benefit in a meaningful subset [67,73]. A more recent ZUMA-2 cohort (cohort 3) evaluating brexu-cel in BTKi-naive relapsed/refractory MCL patients reported an even higher 91% objective response rate with a 73% complete response rate, suggesting potential benefit from earlier CAR-T sequencing in this population [67]. Real-world experience in both the United States (US Lymphoma CAR-T Consortium) and the United Kingdom has generally reproduced ZUMA-2 efficacy and toxicity findings in broader, less-selected patient populations, notably including many patients who would not have met formal ZUMA-2 eligibility criteria, though tumor-intrinsic high-risk features (TP53 aberration, blastoid/pleomorphic

morphology, high Ki-67, complex karyotype) were associated with inferior progression-free survival [69,72].

3.4 Efficacy in B-Cell Acute Lymphoblastic Leukemia

In pediatric and young adult relapsed/refractory B-ALL, the ELIANA trial established tisagenlecleucel with an overall remission rate of 81–82% within three months of infusion. Long-term (approximately 6-year) follow-up demonstrated a 63% overall survival at 3 years and an estimated 5-year relapse-free survival among responders of approximately 47–51%, with no new or unexpected long-term adverse events and continued quality-of-life improvement reported through 36 months post-infusion, supporting tisagenlecleucel's positioning as a potentially curative option for this heavily pretreated population, which historically carries a poor prognosis with conventional salvage chemotherapy [33,34,35,38,40]. As of the most recent regulatory landscape, tisagenlecleucel remains the only CAR T-cell product formally approved for pediatric B-ALL [4].

In adult B-ALL, a population with more resistant leukemia biology and generally inferior outcomes relative to pediatric patients, brexucabtagene autoleucel was established by the ZUMA-3 trial, achieving a complete remission/complete remission with incomplete hematologic recovery rate of 73% (60% CR) and a median overall survival of 25.4 months at three-year follow-up, representing a substantial improvement over historical outcomes with salvage chemotherapy in this setting [36,39]. Real-world CIBMTR registry data on tisagenlecleucel in B-ALL, representing the largest data set assembled for any CAR T-cell product in this population, have shown effectiveness and safety consistent with ELIANA, while also suggesting that tisagenlecleucel may carry a lower risk of severe ICANS relative to brexucabtagene autoleucel in young adult patients, based on comparative registry analysis (grade ≥3 ICANS 24% with real-world brexu-cel versus rates more consistent with tisa-cel's established profile) [39].

3.5 Cytokine Release Syndrome and Immune Effector Cell-Associated Neurotoxicity Syndrome

CRS and ICANS are the defining acute toxicities of CD19 CAR T-cell therapy, arising from the massive, synchronized activation and proliferation of infused CAR T cells and the resulting systemic release of inflammatory cytokines, principally interleukin-6 (IL-6) [41,46]. CRS typically manifests within the first one to two weeks after infusion with fever, hypotension, hypoxia, and, in severe cases, capillary leak and disseminated intravascular coagulation resembling macrophage activation syndrome/hemophagocytic lymphohistiocytosis; ICANS, which may occur concurrently with or following CRS, presents as an inflammatory encephalopathy ranging from mild confusion and word-finding difficulty to obtundation, seizures, and, rarely, life-threatening cerebral edema, reflecting impaired blood-brain barrier integrity under the same inflammatory cytokine pressure [44,46].

The 2019 American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading system harmonized what had previously been at least six different institution- and trial-specific grading approaches (including the earlier CARTOX-10 system) into a single framework based on fever, hypotension, and hypoxia severity for CRS, and on the Immune Effector Cell-Associated Encephalopathy (ICE) score, level of consciousness, seizure activity, motor findings, and radiographic evidence of raised intracranial pressure/cerebral edema for ICANS [42,44,48]. This standardization has enabled valid cross-trial and

cross-product comparison of toxicity incidence for the first time in the field's history.

Management of CRS centers on tocilizumab, an IL-6 receptor antagonist that received concurrent FDA approval alongside the first CAR-T product specifically for this indication, with or without corticosteroids depending on severity and persistence of symptoms; refractory CRS may require second-line anticytokine agents such as siltuximab, anakinra (an IL-1 receptor antagonist), or tumor necrosis factor inhibitors [41,43]. ICANS management relies primarily on corticosteroids, as tocilizumab's poor central nervous system penetration limits its direct efficacy against neurotoxicity and, notably, tocilizumab administration can transiently increase serum IL-6 concentrations through impaired receptor-mediated clearance, a mechanistic consideration relevant to refractory neurotoxicity management [43,47]. There is growing interest in prophylactic or preemptive strategies (early or risk-adapted tocilizumab, prophylactic corticosteroids, and investigational IL-1 blockade with anakinra) aimed at reducing severe toxicity incidence without compromising antitumor efficacy [11,41,47].

Toxicity incidence varies meaningfully by CAR construct and disease context. In ZUMA-1, grade ≥3 CRS and neurologic events occurred in 11% and 31% of patients, respectively, with any-grade neurotoxicity reported in 64% of patients (28% grade ≥3); by comparison, JULIET reported any-grade neurotoxicity in only 21% of patients (12% grade ≥3), a difference initially attributed to the more rapid CAR T-cell expansion associated with CD28 costimulation in axi-cel relative to the 4-1BB costimulation used in tisa-cel [11,46]. A multicenter Greek toxicity-management survey across 173 adult patients receiving axi-cel, tisa-cel, and brexu-cel similarly found grade ≥3 CRS incidence of 6.6%, 3.3%, and 10% respectively, reinforcing this construct-dependent toxicity gradient in real-world practice [45].

3.6 Mechanisms of Resistance and Relapse

Despite high initial response rates, a substantial proportion of patients who respond to CD19 CAR T-cell therapy ultimately relapse. Resistance mechanisms are broadly divided into CAR T-cell-intrinsic failures — inadequate manufacturing, insufficient in vivo expansion, or limited persistence — and tumor-intrinsic antigen-dependent resistance, of which CD19 antigen loss ("antigen escape") is the dominant and best-characterized mechanism, implicated in relapse in more than 40% of patients undergoing CD19 CAR-T therapy in some series [51,54,57].

CD19 loss arises through several convergent molecular mechanisms: genetic mutations and frameshift alterations affecting CD19 exons 2–5, which encode residues critical for recognition by the FMC63 scFv used in most approved constructs; aberrant alternative splicing (particularly loss of exon 2, often related to reduced expression of the splicing factor SRSF3) producing a truncated, non-functional CD19 protein lacking the relevant extracellular epitope or transmembrane anchor; outgrowth of a pre-existing CD19-negative malignant subclone under CAR T-cell selective pressure, with retrospective analysis of 628 B-ALL samples finding CD19-negative tumor populations already present in approximately 17% of patients prior to any CAR-T exposure; epigenetic silencing via CD19 promoter hypermethylation, described in chronic lymphocytic leukemia and Burkitt lymphoma; and, less commonly, lineage switch, in which CAR T-cell selective pressure drives reprogramming or dedifferentiation of the malignant clone away from the B-cell lineage entirely [49,52,55,56].

Notably, the choice of CAR costimulatory domain appears to independently influence the trajectory of antigen escape: in vitro and mathematical modeling work has demonstrated that CD19–4-1BB CAR-T cells (as in tisagenlecleucel) are more

prone to driving combined epitope/total-protein CD19 loss and consequent resistance against low-antigen-density tumor cells than CD19–CD28 CAR-T cells (as in axicabtagene ciloleucel), offering a mechanistic explanation for observed clinical differences in relapse patterns between these two constructs and highlighting CAR design itself as a modifiable contributor to resistance risk, not merely a determinant of toxicity [49,50].

3.7 Real-World Evidence

A substantial and growing body of real-world evidence, drawn from large multinational registries including CIBMTR (United States/Canada), DESCAR-T (France), GELTAMO/GETH (Spain), the German Lymphoma Alliance/DRST registry, and the UK national registry, has generally validated the efficacy and safety profiles established in pivotal trials, extending these findings to broader, more heterogeneous, and often more heavily comorbid patient populations than those enrolled in registrational studies; one CIBMTR analysis found that only 43.0% of real-world axi-cel recipients would have met formal ZUMA-1 trial eligibility criteria, underscoring how much more inclusive routine clinical practice has become relative to the original trial populations [84].

A systematic review and meta-analysis of real-world CD19 CAR T-cell outcomes in large B-cell lymphoma found response and survival outcomes broadly consistent with pivotal trial data across dozens of published cohorts internationally [77,84]. More granular comparative real-world analyses have begun to surface product-level differences not directly testable in randomized trials: a multicenter retrospective cohort of 624 patients treated with axi-cel, tisa-cel, or liso-cel found that tisa-cel was associated with inferior survival relative to the other two products, while liso-cel demonstrated the most favorable toxicity profile and lowest resource utilization for toxicity management, broadly consistent with the construct-based toxicity gradient described above [81]. Real-world CIBMTR data specifically in mantle cell lymphoma (500 patients treated with commercial brexu-cel) and in the rarer primary mediastinal B-cell lymphoma subtype have similarly reported effectiveness and safety outcomes concordant with pivotal trial results, reinforcing external validity of the pivotal evidence base across most major B-cell malignancy subtypes [75,76,78].

3.8 Cost, Manufacturing, and Access Barriers

Despite this favorable and expanding efficacy and safety evidence base, access to CD19 CAR T-cell therapy remains highly unequal. List prices for approved products range from approximately $373,000 to $475,000 depending on the specific product and indication, and total episode-of-care costs — incorporating drug acquisition, apheresis, lymphodepletion, inpatient toxicity monitoring and management, and, in some cases, treatment of severe CRS/ICANS requiring intensive care — can approach $1–2 million per patient in the United States [58,64]. A recent access-barriers framework identifies four principal domains limiting equitable global implementation: cost and reimbursement structures, regulatory approval pathways, manufacturing logistics (including the multi-week vein-to-vein manufacturing time during which clinically deteriorating patients may become ineligible), and clinical infrastructure required for safe toxicity monitoring and management, with these barriers disproportionately affecting patients in low- and middle-income countries and underserved populations within high-income health systems alike [59,60,62].

One US-based analysis found that only 7.3% of CAR-T-related hospital admissions involved patients from neighborhoods with a mean household income below $40,000, illustrating the

socioeconomic gradient in real-world access even within a single high-income health system, despite the existence of manufacturer-sponsored financial assistance programs whose awareness among treating providers remains inconsistent [66]. Emerging solutions include decentralized, point-of-care manufacturing using closed automated systems (e.g., CliniMACS Prodigy), which academic programs in Brazil, India, Turkey, and Spain have demonstrated can reduce manufacturing costs to approximately 20–30% of commercial product pricing; in India specifically, locally manufactured CAR-T products have achieved costs in the range of $25,000–$50,000, driven substantially by lower labor and material costs alongside targeted government subsidy programs, offering a proof-of-concept pathway toward broader global access [60,62,65].

3.9 Next-Generation Approaches

Two broad strategies dominate current efforts to extend the benefit of CD19 CAR T-cell therapy and address its principal limitations of antigen-escape relapse and restricted access. First, dual- and multi-antigen CAR constructs, most commonly combining CD19 with CD22 (and, less commonly, CD20 or CD79b) targeting, are designed to prevent single-antigen escape by requiring simultaneous loss of two independent surface antigens for the malignant clone to evade recognition; early-phase trials of bispecific CD19/CD22 constructs in relapsed/refractory B-ALL and large B-cell lymphoma have reported high response rates (up to 100% ORR in B-ALL in one phase 1 cohort) with encouraging safety profiles, though relapses in these trials have still been associated predominantly with loss of CD19 rather than CD22, suggesting that truly balanced dual-antigen potency remains an unresolved engineering challenge [85,88,90,93,94]. A 2025 ESMO-presented phase 2 trial of a dual CD19/CD22 construct (CAR2219) in relapsed/refractory large B-cell lymphoma reported a 100% overall response rate with a 67.7% complete response rate and a predominantly low-grade CRS toxicity profile, representing one of the more mature dual-antigen efficacy signals reported to date [85].

Second, allogeneic ("off-the-shelf") CAR T-cell platforms, manufactured in advance from healthy donor T cells and gene-edited to reduce graft-versus-host disease and immune rejection risk, aim to eliminate the multi-week manufacturing wait inherent to autologous products and thereby both reduce cost through economies of scale and enable treatment of rapidly progressive patients who might otherwise become ineligible during autologous manufacturing; clinical results for allogeneic CAR-T in B-cell malignancies to date have been comparatively modest relative to autologous products, reflecting ongoing challenges with in vivo persistence and allogeneic rejection, though novel approaches incorporating additional gene-edited "protective" receptors (e.g., CD70-directed constructs designed to eliminate alloreactive host lymphocytes) are in early clinical development [86,87,91]. Beyond hematologic malignancies, logic-gated and dual-receptor CAR designs are also beginning to inform strategies for extending CAR-T principles to solid tumors, illustrating the broader trajectory of the field beyond its original CD19 B-cell malignancy indications [91].

4. SUMMARY OF APPROVED CD19-DIRECTED CAR T-CELL PRODUCTS

Table 1 summarizes the five FDA-approved CD19-directed CAR T-cell products relevant to B-cell lymphoma and leukemia discussed in this review, together with their costimulatory domain, principal approved indications, and key pivotal-trial efficacy findings synthesized above.

Table 1. Approved CD19-directed CAR T-cell products in B-cell lymphoma and leukemia

Product (brand)	Costimulatory domain	Principal indication(s)	Key pivotal trial(s)	Headline efficacy finding
Tisagenlecleucel (Kymriah)	4-1BB	R/R DLBCL (3L+); R/R FL; pediatric/young adult R/R B-ALL	JULIET; ELARA; ELIANA	ELIANA: 63% 3-yr OS in B-ALL; JULIET: 32% 60-mo OS overall
Axicabtagene ciloleucel (Yescarta)	CD28	R/R LBCL (3L+ and 2L early relapse/refractory); R/R indolent NHL (FL)	ZUMA-1; ZUMA-7; ZUMA-5	ZUMA-1: 43% 5-yr OS; ZUMA-7: 54.6% vs 46.0% 4-yr OS vs SOC
Lisocabtagene maraleucel (Breyanzi)	4-1BB	R/R LBCL (3L+ and 2L)	TRANSCEND NHL 001; TRANSFORM	Comparable long-term survival to tisa-cel on MAIC; favorable toxicity profile
Brexucabtagene autoleucel (Tecartus)	CD28	R/R mantle cell lymphoma; adult R/R B-ALL	ZUMA-2; ZUMA-3	ZUMA-2: 93% ORR/67% CR in MCL; ZUMA-3: 60% CR, 25.4-mo median OS in adult B-ALL
Obecabtagene autoleucel (Aucatzyl)	4-1BB	Adult R/R B-ALL	FELIX	Newest approved CD19 product in adult B-ALL (2024)

DISCUSSION

This review synthesizes a decade of accumulating evidence supporting CD19-directed CAR T-cell therapy as a transformative, and in a meaningful subset of patients genuinely curative, treatment for relapsed or refractory B-cell lymphoma and leukemia. Several cross-cutting themes emerge from this synthesis with direct implications for clinical practice and future research priorities.

First, the field's center of gravity has shifted decisively earlier in the treatment sequence for large B-cell lymphoma. Where CD19 CAR T-cell therapy was originally validated only in heavily pretreated, third-line-or-later patients, the randomized phase 3 ZUMA-7 and TRANSFORM trials have established superiority over standard second-line autologous transplantation for early relapsed or primary refractory disease, a genuinely practice-changing result supported by one of the only overall-survival-positive randomized comparisons in this therapeutic area to date. This shift carries important implications for referral pathways: because CAR-T manufacturing requires several weeks and disease progression during this window can render patients ineligible, the ZUMA-7 experience argues for earlier hematology-oncology and cellular-therapy-center referral discussion at the point of first relapse or primary refractory disease identification, rather than deferring referral until later treatment lines have been exhausted.

Second, the maturation of standardized CRS/ICANS grading (ASTCT consensus criteria) and management algorithms (tocilizumab and corticosteroids, with risk-adapted and prophylactic strategies increasingly under investigation) represents a genuine advance in the safety profile

of this therapy, but toxicity remains construct-dependent in a way that carries direct clinical decision-making relevance: the higher toxicity but potentially more potent, faster-expanding profile of CD28-costimulated constructs (axi-cel, brexu-cel) versus the more gradual, better-tolerated but potentially more resistance-prone profile of 4-1BB-costimulated constructs (tisa-cel, liso-cel) is not simply an efficacy-versus-safety trade-off but appears mechanistically linked to differential antigen-escape trajectories, suggesting that costimulatory domain selection may eventually be individualized based on patient-specific risk factors for toxicity versus relapse rather than treated as an interchangeable design choice.

Third, antigen escape remains the single most important unresolved efficacy-limiting mechanism in this field, and the evidence synthesized here suggests it is not a stochastic or uniform process but one shaped by CAR construct design, pre-existing tumor clonal heterogeneity, and epitope-specific selective pressure. This mechanistic specificity is encouraging from a therapeutic-development standpoint: it suggests that antigen escape is, at least in principle, a rationally addressable engineering problem, and the early clinical data on dual-antigen CD19/CD22 constructs — while still preliminary and still demonstrating CD19-predominant relapse patterns even in "dual-target" designs — represent a genuine, mechanistically grounded attempt to close this gap rather than an incremental modification.

Fourth, and perhaps most consequentially for global health equity, the persistent and in some analyses worsening gap between the demonstrated clinical efficacy of CD19 CAR-T therapy and its real-world accessibility represents an ethical and health-systems challenge as significant as any remaining scientific question in the field. The finding that CAR-T-related hospital admissions are disproportionately concentrated among higher-income patients even within a single, high-income health system, combined with the near-total absence of access in large parts of Africa and Asia, indicates that the benefits demonstrated in this review's pivotal trials remain substantially inaccessible to the global majority of patients who could clinically benefit from this therapy. The emerging evidence that decentralized, academically manufactured CAR-T products can achieve costs an order of magnitude lower than commercial list prices, as demonstrated in India, Brazil, and elsewhere, is among the most practically important findings synthesized in this review, and warrants substantially greater research and policy investment relative to its current profile in the mainstream CAR-T literature, which remains weighted heavily toward incremental efficacy and toxicity refinements in already-well-resourced health systems.

5.1 Limitations of This Review

As a narrative rather than systematic review, this synthesis is subject to selection and availability bias in source identification, and formal quantitative pooling (meta-analysis) of efficacy or toxicity estimates across trials was not performed given the substantial heterogeneity in patient populations, prior treatment exposure, and outcome definitions across the cited studies. Cross-product efficacy and safety comparisons rely substantially on matching-adjusted indirect comparisons and retrospective real-world cohorts rather than randomized head-to-head trials, which do not exist for most product pairs discussed; such indirect evidence, while informative, cannot fully account for unmeasured confounding, including center-level differences in toxicity management practice and patient selection. Long-term (beyond 5-year) follow-up data remain available for only a subset of approved products and indications, and conclusions regarding "curative potential" should be understood as applying to a meaningful subset

of complete responders rather than to the treated population as a whole. Finally, this review's cost and access analysis draws primarily on United States and European sources supplemented by emerging-economy manufacturing reports, and a more granular, region-specific analysis would be needed to fully characterize access barriers across the full range of low- and middle-income health system contexts.

CONCLUSION

CD19-directed CAR T-cell therapy has fundamentally changed the treatment landscape for relapsed or refractory B-cell lymphoma and leukemia, with five approved products now supported by pivotal trial evidence extending to five and, in one case, ten years of follow-up, and with second-line efficacy in large B-cell lymphoma now established through randomized, overall-survival-positive phase 3 trials. Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome are now managed within a standardized, increasingly refined framework, though toxicity risk remains meaningfully construct-dependent. Antigen escape remains the dominant mechanism limiting durable benefit and is the central target of next-generation dual-antigen and allogeneic platform development. Real-world registry evidence has largely validated pivotal trial findings in broader populations, lending confidence to the generalizability of this evidence base. The most pressing unresolved challenge is not scientific but structural: the cost and manufacturing complexity of CAR T-cell therapy continue to restrict its benefit to a fraction of the global patient population who could clinically benefit, and closing this access gap, through decentralized manufacturing, value-based reimbursement models, and expanded international regulatory and infrastructure capacity, should be regarded as a priority of equal importance to continued efficacy and toxicity refinement within the field.

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ETHICS APPROVAL

This is a narrative literature review that did not involve primary data collection from human or animal subjects; therefore, institutional ethics committee approval was not applicable to this work.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DECLARATION OF ORIGINALITY

This manuscript has not been published previously and is not under consideration for publication elsewhere, in whole or in part, in any language.

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