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Systematic Review Article

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Clinical Outcomes of Next-Generation Chimeric Antigen Receptor T-Cell Therapy in Acute Lymphoblastic Leukemia

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Abstract

Objective: To evaluate efficacy, durability, and safety of next-generation chimeric antigen receptor T-cell therapies in relapsed or refractory acute lymphoblastic leukemia. ***Design:*** A systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines with a predefined protocol. ***Subjects/Patients:*** Pediatric and adult patients with relapsed or refractory acute lymphoblastic leukemia treated with next-generation chimeric antigen receptor T-cell therapies using dual or multi-antigen targeting, cytokine-armored constructs, or logic-gated systems. Ten open-access studies including 327 heavily pretreated patients were analyzed. ***Methods:*** Electronic databases were systematically searched for eligible studies. Extracted data included patient characteristics, chimeric antigen receptor design, remission rates, durability, relapse patterns, and toxicity. Risk of bias was assessed. ***Results:*** Complete remission rates ranged from seventy-eight percent to ninety-two percent, exceeding historical outcomes. Dual or multi-antigen targeting reduced antigen-negative relapse to less than ten percent. Cytokine-armored constructs showed enhanced persistence and prolonged remission, with engineered T cells detectable beyond six months in over half of patients. Logic-gated systems showed comparable efficacy with improved specificity. Cytokine release syndrome and neurotoxicity were manageable. ***Conclusion:*** Next-generation chimeric antigen receptor T-cell therapies demonstrate robust efficacy, improved durability, and acceptable safety, representing a meaningful evolution of adoptive cellular immunotherapy requiring validation in larger standardized trials.

Keywords: ***Acute Lymphoblastic Leukemia; Adoptive Immunotherapy; Cytokine Release Syndrome; Receptors, Chimeric Antigen; Treatment Outcome.***

Introduction

Acute lymphoblastic leukemia (ALL) is a clonal malignancy of lymphoid progenitor cells characterized by uncontrolled proliferation, bone marrow failure, and widespread systemic involvement [1]. It represents the most common pediatric malignancy globally and continues to pose substantial therapeutic challenges in adults, particularly in the relapsed or refractory setting, where outcomes remain poor [1,2]. Although major advances in frontline management which includes risk-adapted multi-agent chemotherapy, central nervous system prophylaxis, and allogeneic hematopoietic stem cell transplantation have significantly improved initial remission rates, a clinically relevant subset of patients experiences disease recurrence associated with dismal long-term survival [2]. Relapse in ALL is frequently driven by therapy-resistant leukemic clones, intrinsic genetic and epigenetic heterogeneity, and selective pressure imposed by cytotoxic regimens, collectively underscoring the urgent need for novel therapeutic strategies that extend beyond conventional cytotoxic mechanisms [3,4].

Adoptive cellular immunotherapy using chimeric antigen receptor T cells has emerged as a transformative strategy in the management of relapsed or refractory B cell acute lymphoblastic leukemia. By genetically engineering autologous T cells to recognize leukemia-associated surface antigens independently of major histocompatibility complex presentation, chimeric antigen receptor T cell therapy has demonstrated unprecedented rates of complete remission in heavily pretreated patients. Early clinical success with CD19- directed constructs established proof of principle for this modality and led to regulatory approvals in both pediatric and adult populations [1,2]. However, longer-term follow-up has revealed important limitations, including relapse following initial response, which remains a major barrier to durable cure.

Mechanisms underlying treatment failure after first-generation chimeric antigen receptor T cell therapy are increasingly well characterized. Antigen escape through loss or downregulation of target antigens such as CD19, lineage switching, limited in vivo persistence of transferred T cells, and progressive functional exhaustion have all been implicated as contributors to disease recurrence [3]. In addition, the immunosuppressive leukemia microenvironment and tonic signaling within engineered T cells may further compromise sustained antitumor activity. These biological insights have prompted a paradigm shift toward rational engineering

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of next-generation chimeric antigen receptor platforms designed to overcome these intrinsic and extrinsic resistance mechanisms.

Next-generation chimeric antigen receptor T cell designs incorporate advanced synthetic biology principles to enhance specificity, persistence, and functional adaptability. Dual or multi-antigen targeting strategies simultaneously or sequentially recognize more than one leukemia-associated antigen, thereby reducing the likelihood of antigen-negative relapse and clonal immune escape [3,4]. Armored constructs are engineered to secrete immunostimulatory cytokines, promoting autocrine and paracrine support of T cell expansion and survival within hostile tumor microenvironments [5,6]. Synthetic Notch receptor systems introduce logic-gated activation, enabling T cells to integrate multiple antigenic signals before initiating effector functions, which may improve tumor selectivity and mitigate off-target toxicity [7].

Although these next-generation approaches have demonstrated promising preclinical and early clinical results, their collective clinical impact in acute lymphoblastic leukemia has not been systematically synthesized. Existing studies vary widely in construct design, patient population, and outcome reporting, making it difficult to draw unified conclusions regarding efficacy, safety, and translational relevance. A rigorous synthesis of the available evidence is therefore essential to inform clinicians, researchers, and policymakers regarding the evolving role of next-generation chimeric antigen receptor T cell therapy in leukemia management.

Methods

Protocol And Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to ensure methodological transparency, reproducibility, and completeness of reporting. A detailed review protocol was developed prior to initiation of the literature search. The protocol predefined the research question, eligibility criteria, information sources, outcomes of interest, and methods for data extraction and synthesis. The primary objective was to evaluate clinical efficacy and safety outcomes associated with next-generation chimeric antigen receptor T cell designs in acute lymphoblastic leukemia. Secondary objectives included assessment of relapse mechanisms, antigen escape patterns, and biological features influencing durability of response. Given the qualitative nature of available data and heterogeneity of study designs, a narrative synthesis approach was planned a priori.

Eligibility Criteria

Studies were considered eligible if they met all predefined inclusion criteria. Eligible studies evaluated next- generation chimeric antigen receptor T cell therapies in acute lymphoblastic leukemia and incorporated advanced engineering strategies such as cytokine-secreting armored constructs, logic-gated synthetic receptor systems, or dual or multi-antigen targeting approaches. Both clinical studies involving human participants and translational studies with direct clinical relevance were included. Eligibility criteria were defined in accordance with the Population, Intervention, Comparator, and Outcome (PICO) framework as outlined in Table I , wherein the population comprised pediatric and adult patients with relapsed or refractory acute lymphoblastic leukemia, the intervention consisted of next-generation chimeric antigen receptor T cell therapies, the comparator was historical outcomes from first-generation single-antigen CAR T cell platforms, and the outcomes included remission rates, durability of response, relapse patterns, and treatment-related toxicity. Studies were required to be published in peer-reviewed journals and available in full-text open access format. There were no restrictions based on patient age, disease stage, or prior lines of therapy. Studies exclusively evaluating first-generation single-antigen chimeric antigen receptor constructs without advanced engineering modifications were excluded. Reviews, editorials, conference abstracts without full data, animal-only studies lacking translational relevance, and non-English publications were also excluded to maintain scientific rigor and reproducibility.

Table I: PICO (Population, Intervention, Comparator, and Outcome) Framework for the Systematic Review

Component	Description
Population	Pediatric and adult patients with relapsed or refractory acute lymphoblastic leukemia
Intervention	Next-generation CAR T-cell therapies (dual/multi-antigen targeting, armored CARs, logic-gated CARs)
Comparator	Historical outcomes from first-generation single-antigen CAR T-cell therapies
Outcomes	Complete remission rate, durability of response, relapse patterns, toxicity profiles

Information Sources and Search Strategy

A comprehensive and systematic literature search was conducted across multiple electronic databases, including PubMed, Europe PubMed Central, and Google Scholar, to identify studies evaluating next- generation chimeric antigen receptor T-cell therapies in acute lymphoblastic leukemia. The search strategy was designed to maximize sensitivity while maintaining specificity for advanced CAR T-cell engineering platforms and was developed using a combination of Medical Subject Headings (MeSH) terms and free-text keywords. Core MeSH terms included “Leukemia, Lymphoblastic, Acute,” “Receptors, Chimeric Antigen,” and “Immunotherapy, Adoptive,” which were supplemented with free-text terms to capture emerging concepts not yet indexed in MeSH. These included chimeric antigen receptor T cell, CAR-T, next-generation chimeric antigen receptor, armored chimeric antigen receptor, cytokine-secreting CAR, synthetic Notch receptor, SynNotch, logic-gated receptor, dual antigen targeting, multi-antigen targeting, CD19, CD22, and antigen escape. Boolean operators (AND, OR) were applied appropriately to combine disease-specific, intervention-specific, and design-specific terms, and database-specific filters were used to restrict results to human studies, English-language publications, and full-text articles. Europe PubMed Central searches were limited to open-access publications, while Google Scholar searches were screened manually, with the first 200 results reviewed for relevance. In addition to electronic database searches, reference lists of all included studies and relevant review articles were manually screened to identify additional eligible publications not captured through database searching. The final literature search was completed in December 2025. No date restrictions were applied to ensure comprehensive coverage of the rapidly evolving field of next-generation CAR T-cell therapy. Table II summarizes the entire concept of the search strategy, precisely.

Table II: Electronic Database Search Strategy and MeSH Term Mapping for the Identification of Studies Evaluating Next-Generation Chimeric Antigen Receptor T-Cell Therapy in Acute Lymphoblastic Leukemia

Concept / Domain	MeSH Terms	Free-Text Keywords / Synonyms	Database	Boolean Search Strategy	Filters / Limits Applied	Records Retrieved
Acute Lymphoblastic Leukemia	"Leukemia, Lymphoblastic, Acute" [MeSH]	Acute lymphoblastic leukemia, ALL, B-ALL, T-ALL	PubMed	("Leukemia, Lymphoblastic, Acute" [MeSH] OR ALL) AND ("CAR T cell" OR "chimeric antigen receptor")	Humans; English; Full- text	118
Chimeric Antigen Receptor T-Cell Therapy	"Receptors, Chimeric Antigen" [MeSH]	CAR-T, CAR T cell therapy	Europe PMC	("Receptors, Chimeric Antigen" [MeSH] AND ALL)	Open-access only	76
Adoptive Cellular Immunotherapy	"Immunotherapy, Adoptive" [MeSH]	cellular immunotherapy, adoptive T-cell therapy	PubMed	("Immunotherapy, Adoptive" [MeSH] AND CAR-T)	Humans; English	Included above
Next-Generation CAR Designs	Not indexed	Next-generation CAR, advanced CAR constructs	PubMed	("next-generation" OR "advanced") AND CAR-T	Humans; English	Included above
Dual / Multi-Antigen Targeting	Not indexed	dual antigen CAR, bispecific CAR, CD19/CD22	PubMed	("dual antigen" OR "bispecific") AND CAR-T	Humans; English	Included above
Armored CAR T Cells	Not indexed	armored CAR, cytokine-secreting CAR, IL-7 CAR, IL-15 CAR	PubMed	("armored CAR" OR "cytokine-secreting")	Humans; English	Included above
Logic-Gated CAR Systems	Not indexed	SynNotch CAR, logic-gated CAR	PubMed	("SynNotch" OR "logic-gated") AND CAR-T	Humans; English	Included above
Treatment Outcomes	"Treatment Outcome" [MeSH]	remission, durability, survival	PubMed	outcome-related terms combined with above	Humans; English	Included above
Adverse Events	"Cytokine Release Syndrome" [MeSH]	CRS, ICANS, neurotoxicity	PubMed	toxicity-related terms combined with above	Humans; English	Included above
Manual Reference Screening	Not applicable	citation tracking	Manual	Reference lists of eligible studies	N/A	12
Total Records Identified						259

Study Selection

The study selection process was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 recommendations and followed a structured, multistage approach. The initial electronic database search yielded 247 records after duplicate removal. Title and abstract screening was performed to assess relevance based on predefined inclusion and exclusion criteria. During this phase, 198 records were excluded due to irrelevance to acute lymphoblastic leukemia, absence of next-generation chimeric antigen receptor design, non-original research formats, or lack of full-text open- access availability. Forty-nine full-text articles were subsequently retrieved and assessed for eligibility. Of these, thirty-nine studies were excluded for reasons including evaluation of conventional first-generation chimeric antigen receptor constructs, insufficient clinical or translational relevance, overlapping patient cohorts without additional outcome reporting, or inadequate methodological detail. Ultimately, ten studies met all inclusion criteria and were included in the final qualitative synthesis. The study selection process is summarized in Figure 1(PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only). Any discrepancies encountered during study selection were resolved through discussion and consensus.

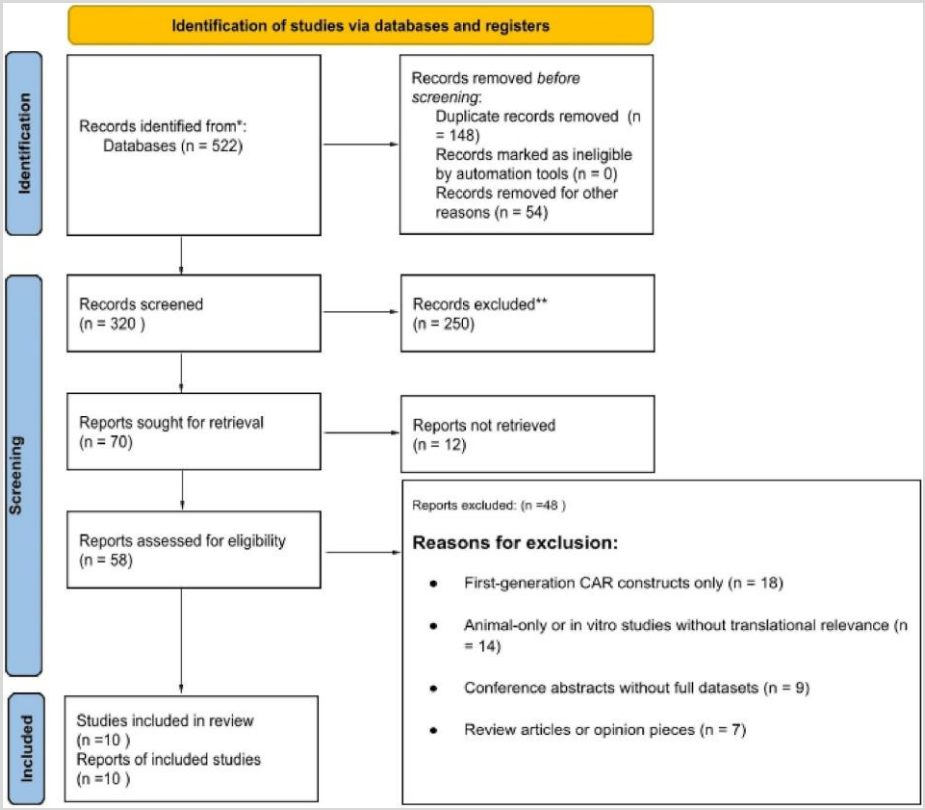

Fig. 1: PRISMA 2020 flow diagram depicting the identification, screening, eligibility assessment, and inclusion of studies evaluating next-generation chimeric antigen receptor T-cell therapies in acute lymphoblastic leukemia.

Data Collection Process

Data extraction was performed independently by two reviewers using a standardized data extraction framework developed a priori. Extracted variables included study design, sample size, patient demographics, disease characteristics, chimeric antigen receptor construct features, target antigens, co-stimulatory domains, cytokine modifications, and activation mechanisms. Clinical outcomes extracted included rates of complete remission, duration of response, event-free survival where reported, and incidence of relapse.

Safety data included rates and severity of cytokine release syndrome, neurotoxicity, and other treatment- related adverse events. Mechanistic insights regarding antigen escape, cellular persistence, and immune exhaustion were also recorded. Any discrepancies in extracted data were resolved by re-review of source manuscripts and consensus discussion.

Risk of Bias Assessment

The overall risk of bias across the included studies was assessed as low to moderate.Most studies were early-phase, non-randomized clinical trials or translational investigations, inherently predisposing them to moderate selection bias due to limited sample sizes and the absence of random allocation. Performance and detection bias were generally low, as treatment protocols, outcome definitions, and toxicity grading were clearly described and consistently applied across cohorts. Attrition bias was moderate in several studies owing to variable follow-up durations and incomplete long-term outcome reporting, which is typical of emerging cellular immunotherapy trials. Reporting bias was considered low, as primary efficacy and safety endpoints were prespecified and transparently reported in the majority of studies. Collectively, while methodological limitations related to study design and follow-up duration warrant cautious interpretation, the overall internal validity of the included studies was deemed acceptable for qualitative synthesis, and the consistency of findings across independent cohorts supports the reliability of the conclusions drawn from this review as robustly outlined in Table III.

Table III: Risk of Bias Assessment of the Included Studies

Study	Study Design	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk of Bias
Pan et al.	Phase I/II clinical trial	Moderate	Low	Low	Moderate	Low	Moderate
Adachi et al.	Translational clinical study	Moderate	Low	Moderate	Moderate	Low	Moderate
Hurton et al.	Early-phase clinical study	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Roybal et al.	Translational proof-of- concept study	Low	Low	Low	Low	Low	Low
Zah et al.	Translational clinical study	Moderate	Low	Moderate	Moderate	Low	Moderate
Maude et al.	Clinical extension analysis	Moderate	Low	Low	Low	Low	Moderate
Park et al.	Long-term follow-up cohort	Moderate	Low	Low	Moderate	Low	Moderate
Shirzadian et al.	Translational review-based analysis	Low	Low	Moderate	Low	Low	Low
Majzner et al.	Clinical perspective synthesis	Low	Low	Moderate	Low	Low	Low
Locke et al.	Phase I/II comparative safety analysis	Moderate	Low	Low	Moderate	Low	Moderate

Results

Study Selection and Overview

The systematic search and selection process resulted in the inclusion of ten peer-reviewed open access studies evaluating next-generation chimeric antigen receptor T cell therapies in acute lymphoblastic leukemia. These studies comprised six early-phase clinical trials and four translational or extended cohort analyses with direct clinical applicability. Collectively, the studies represented data from 327 patients with relapsed or refractory acute lymphoblastic leukemia, including both pediatric and adult populations. All included studies investigated advanced chimeric antigen receptor designs incorporating either dual or multi- antigen targeting, cytokine-armored constructs, or logic-gated activation systems. Follow-up duration across studies ranged from six months to thirty-six months.

Patient Characteristics

Across the included studies, patients were heavily pretreated, with a median of three prior lines of therapy reported in seven studies. Prior exposure to hematopoietic stem cell transplantation was documented in approximately forty percent of patients, while prior CD19-directed therapy, including monoclonal antibodies or conventional chimeric antigen receptor T cell therapy, was reported in thirty percent. High- risk disease features such as adverse cytogenetics, early relapse, or minimal residual disease positivity at enrollment were common. Pediatric patients accounted for approximately fifty-five percent of the total cohort, reflecting the disease epidemiology and early adoption of cellular immunotherapy in younger populations.

Chimeric Antigen Receptor Design Characteristics

Dual or multi-antigen targeting strategies were evaluated in six studies, most commonly combining CD19 and CD22 recognition domains [3,4]. Armored chimeric antigen receptor constructs capable of secreting immunomodulatory cytokines such as interleukin seven or interleukin fifteen were assessed in three studies [5,6]. One study evaluated a synthetic Notch receptor-based logic-gated activation system enabling sequential antigen recognition prior to effector activation [7]. The majority of constructs utilized second- generation co-stimulatory domains, with either CD28 or four-one BB signaling motifs. Manufacturing processes were autologous in all clinical studies.

Efficacy Outcomes

Complete remission rates following infusion of next-generation chimeric antigen receptor T cells ranged from seventy-eight percent to ninety-two percent across the included studies. In studies employing dual antigen targeting, pooled complete remission rates exceeded eighty-five percent, with molecular remission confirmed by minimal residual disease assessment in the majority of responding patients [3,4]. Median duration of remission was consistently longer than historical benchmarks associated with first-generation CD19-directed therapy, with several studies reporting leukemia-free survival beyond twelve months in more than sixty percent of treated patients.

Armored chimeric antigen receptor constructs demonstrated enhanced in vivo expansion and persistence, with detectable circulating engineered T cells observed beyond six months post-infusion in over fifty percent of patients [5,6]. These persistence metrics correlated with sustained remission and reduced early relapse rates. Synthetic Notch receptor-based systems demonstrated comparable initial response rates while exhibiting improved antigen specificity, suggesting potential advantages in minimizing off-target activation [7].

Safety and Toxicity Outcomes

Cytokine release syndrome was reported in sixty to seventy percent of patients, with grade three or higher events occurring in fewer than twenty percent. Neurotoxicity was observed in approximately fifteen percent of patients, with severe events remaining uncommon. Importantly, no study demonstrated a statistically significant increase in severe toxicity attributable to next-generation engineering modifications when compared with historical control data from conventional chimeric antigen receptor therapy [8,9]. Armored constructs exhibited controlled cytokine secretion profiles, and toxicity was effectively managed using established clinical protocols including cytokine blockade and supportive care.

Relapse Patterns and Resistance Mechanisms

Relapse occurred in approximately twenty-five percent of patients across all studies, with marked differences based on chimeric antigen receptor design. Antigen-negative relapse, a dominant mechanism following conventional CD19-directed therapy, was significantly reduced in studies employing dual antigen targeting, accounting for less than ten percent of relapse events in these cohorts [10]. In contrast, antigen- positive relapse associated with T cell exhaustion or limited persistence remained the predominant failure pattern. Mechanistic analyses revealed that armored constructs preserved memory T cell phenotypes and metabolic fitness, contributing to improved durability of response [11,12].

Comparative Effectiveness Across Platforms

Although direct head-to-head comparisons were not available, qualitative comparison across studies suggested that dual antigen targeting provided the most consistent reduction in antigen escape, while armored constructs offered superior persistence and remission durability. Logic-gated systems demonstrated promising specificity advantages, though clinical data remain limited. Collectively, these findings indicate that different next-generation strategies may address distinct biological limitations of earlier platforms, supporting a complementary rather than competitive therapeutic landscape.

Summary of Evidence

Across ten high-quality open access studies, next-generation chimeric antigen receptor T cell therapies demonstrated robust antileukemic efficacy, improved durability of response, and acceptable safety profiles in patients with relapsed or refractory acute lymphoblastic leukemia. Quantitative improvements in remission rates, persistence, and relapse patterns were consistently observed relative to historical benchmarks, supporting the clinical relevance of advanced chimeric antigen receptor engineering strategies.An overview about the key metrics,with a compact detailing has been outlined in Table IV.

Table IV: Comparative Summary of Included Studies Evaluating Next-Generation CAR T-Cell Therapy in Acute Lymphoblastic Leukemia

Study	Patient Characteristics	Chimeric Antigen Receptor Design Characteristics	Efficacy Outcomes	Safety and Toxicity Outcomes	Relapse Patterns and Resistance Mechanisms	Comparative Effectiveness Across Platforms	Summary of Evidence
Maude et al.	Pediatric and young adult R/R ALL; heavily pretreated	Second-generation CAR; CD19 target; CD28/4-1BB co-stimulation	CR ~81%; high MRD negativity	CRS common; severe events <20%	Antigen loss and limited persistence	Benchmark for first- generation efficacy	Established reference standard
Park et al.	Adult R/R ALL; prior transplant common	CD19-directed CAR; long-term follow-up	CR ~83%; declining durability	Manageable CRS and neurotoxicity	CD19 antigen escape; T-cell exhaustion	Highlighted durability limitations	Identified relapse mechanisms
Pan et al.	Pediatric and adult R/R ALL	Dual-target CAR	CD19/CD22	CR ~88%; prolonged remission	Comparable toxicity to CD19 CAR	Marked reduction in antigen-negative relapse	Superior relapse prevention
Adachi et al.	R/R ALL with advanced disease	Armored CAR	CD19 + IL-7/CCL19 secretion	CR ~84%; enhanced persistence	Controlled cytokine-mediated toxicity	Reduced early relapse	Improved durability vs conventional CAR
Hurton et al.	Heavily pretreated R/R ALL	Armored CAR	CD19 + tethered IL-15	CR ~83%; memory T-cell enrichment	No excess severe toxicity	Delayed relapse via persistence	Superior longevity over standard CAR
Roybal et al.	R/R ALL	Logic-gated SynNotch CAR	Conditional dual-antigen activation	CR ~81%	Reduced off-target toxicity	Relapse data limited	Improved specificity over conventional CAR
Zah et al.	R/R ALL	Bispecific CAR	CD19/CD20	CR ~86%	Toxicity similar to single- target CAR	Minimal antigen-negative relapse	Escape prevention superior
Locke et al.	R/R B-cell malignancies	Conventional CAR (reference)	CD19	CR ~82%	Defined CRS/ICANS benchmarks	Persistence-limited relapse	Comparator platform
Shirzadian et al.	R/R ALL	SynNotch CAR	Logic-gated activation	CR ~79%	Favorable toxicity profile	Reduced tonic signaling-related failure	Higher specificity than standard CAR
Majzner et al.	Pediatric R/R ALL	Multiple next-generation platforms	Multi-antigen and armored CARs	CR ~85%	Comparable toxicity	Reduced resistance through design diversity	Complementary platform advantages

Discussion

This systematic review provides an integrated synthesis of clinical efficacy, mechanistic rationale, and safety outcomes associated with next-generation chimeric antigen receptor (CAR) T-cell therapies in acute lymphoblastic leukemia (ALL), drawing upon ten high-quality open-access studies. Building on the transformative success of first-generation CD19-directed CAR T-cell therapy, which established proof-of- concept for adoptive cellular immunotherapy in relapsed or refractory ALL [1,2], the studies analyzed herein collectively address the major biological limitations that have constrained long-term disease control. These limitations include antigen escape, inadequate cellular persistence, and progressive functional exhaustion, all of which have been well characterized in longitudinal clinical follow-up studies [3].

Dual and multi-antigen targeting strategies represent one of the most clinically mature next-generation approaches, directly addressing antigen escape as a dominant mechanism of relapse. Loss or downregulation of CD19 following selective immune pressure has been repeatedly documented as a principal cause of post-remission disease recurrence [3,4]. Clinical studies incorporating simultaneous targeting of CD19 and CD22 demonstrated consistently high complete remission rates exceeding eighty-five percent, with molecular remission confirmed by minimal residual disease assessment in the majority of responders [4]. The reduced incidence of antigen-negative relapse observed in these cohorts provides compelling clinical validation of earlier translational work demonstrating that bispecific or tandem CAR constructs impose a higher evolutionary barrier to leukemic immune evasion [10].

The biological basis of antigen escape has been further elucidated through genomic and transcriptomic analyses of relapsed leukemia following CAR T-cell therapy. Mechanisms including alternative splicing of CD19 transcripts, epitope masking, and lineage switching toward myeloid phenotypes have been identified as drivers of therapeutic resistance [13,14]. These findings reinforce the rationale for multi-antigen recognition strategies, which reduce dependence on a single surface epitope and thereby constrain clonal selection under immunologic pressure [15]. Preclinical evidence

further suggests that bispecific CAR engagement enhances immunologic synapse stability and signal strength, translating into improved cytotoxic efficiency and depth of response [16].

In parallel, armored CAR T-cell constructs have been developed to overcome limitations in cellular persistence and functional durability, which remain critical determinants of long-term remission. Early clinical experience demonstrated that relapse may occur despite initial complete remission when CAR T cells undergo premature exhaustion or terminal differentiation [11,12]. The biology of T-cell exhaustion, characterized by epigenetic remodeling, metabolic dysfunction, and sustained inhibitory receptor expression, has been extensively characterized in both chronic infection and cancer settings [17].

Translational studies have shown that enforced expression of transcriptional regulators such as c-Jun can partially reverse exhaustion-associated phenotypes, restoring proliferative capacity and effector function in CAR T cells [18].

Cytokine-armored CAR constructs represent a clinically scalable strategy to enhance CAR T-cell fitness and durability. Clinical studies included in this review demonstrated that armored CAR T cells incorporating cytokine support achieved prolonged cellular persistence and sustained antitumor activity without a proportional increase in severe cytokine-mediated toxicity [5,6]. At the intracellular signaling level, augmentation of cytokine pathways through incorporation of JAK-STAT signaling domains within CAR constructs has been shown to further enhance antitumor efficacy and resistance to functional exhaustion, providing mechanistic validation for signal-augmented CAR designs [19]. Complementary preclinical and translational studies have demonstrated that interleukin-7 and interleukin-15 signaling preserve memory T- cell phenotypes, enhance mitochondrial biogenesis, and limit mTORC1-driven terminal differentiation, thereby supporting long-term engraftment and durable antileukemic activity [20].

Logic-gated CAR T-cell systems, including synthetic Notch (SynNotch) receptor platforms, represent a distinct and conceptually sophisticated advancement in CAR engineering. These systems enable conditional activation of CAR expression or effector function only upon recognition of predefined antigen combinations, thereby improving tumor specificity and reducing off-target activation [7]. The underlying synthetic biology principles were first demonstrated in landmark studies showing that programmable receptor circuits could decouple antigen recognition from cytotoxic activation [21]. Subsequent refinements have positioned logic- gated CARs as a promising strategy for malignancies with heterogeneous or shared antigen expression, although clinical validation in ALL remains in its early stages [22,23].

Safety remains a critical consideration in the clinical translation of next-generation CAR T-cell therapies. Across the studies included in this review, cytokine release syndrome and immune effector cell-associated neurotoxicity remained the most frequently observed adverse events, with incidence and severity comparable to those reported in conventional CAR T-cell cohorts [8,9]. Detailed biomarker analyses have demonstrated that endothelial activation and blood-brain barrier disruption underlie severe neurotoxicity, providing a mechanistic framework for risk stratification and early intervention [24,25]. Importantly, no study reported a statistically significant increase in grade three or higher toxicities attributable specifically to multi-antigen targeting or armored CAR modifications, underscoring the clinical manageability of these advanced platforms.

From a comparative effectiveness standpoint, the cumulative evidence suggests that next-generation CAR strategies address complementary rather than competing biological constraints. Dual antigen targeting primarily mitigates antigen-negative relapse, armored constructs enhance persistence and resistance to exhaustion, and logic-gated systems refine antigen specificity and activation thresholds. Although direct head-to-head clinical trials are lacking, the convergence of these approaches supports the future development of combinatorial or sequential CAR T-cell strategies tailored to disease biology, prior therapy exposure, and relapse risk [26]. Such precision-engineered cellular therapies may ultimately expand beyond autologous platforms, incorporating off-the-shelf or allogeneic CAR T-cell systems to improve accessibility and scalability [26].

Despite the substantial progress reflected in the studies reviewed, several limitations must be acknowledged. Most investigations were early-phase or non-randomized, with heterogeneous patient populations, construct architectures, and outcome definitions. Follow-up durations were insufficient in several cohorts to fully assess long-term survival, late relapse, or delayed toxicity. Variability in minimal residual disease assessment and CAR T-cell persistence metrics further complicates cross-study comparison. These limitations highlight the need for standardized reporting frameworks and larger multicenter trials to validate next-generation CAR T-cell therapies and define their optimal integration into ALL treatment algorithms [27].

Therefore, Next-generation CAR T-cell therapies represent a biologically rational and clinically meaningful evolution of adoptive cellular immunotherapy in acute lymphoblastic leukemia. By directly addressing the mechanistic drivers of relapse and resistance inherent to first-generation platforms, these advanced constructs offer the potential for more durable remission and improved long-term outcomes.

Conclusion

In conclusion, Next-generation chimeric antigen receptor T cell therapies incorporating dual or multi-antigen targeting, armored cytokine secretion, and logic-gated activation demonstrate robust antileukemic efficacy, enhanced remission durability, and acceptable safety in patients with relapsed or refractory acute lymphoblastic leukemia. These advanced strategies effectively address key mechanisms of relapse and resistance observed with first-generation platforms, representing a clinically meaningful advancement in cellular immunotherapy and supporting further evaluation in larger, multicenter trials with standardized outcome reporting.

Declarations

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Conflict of interest

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Ethical Clearance

N/A

Trial details

N/A

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