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LATEST ADVANCES IN THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA: A NARRATIVE REVIEW OF NOVEL TARGETED AND IMMUNOTHERAPEUTIC STRATEGIES

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ABSTRACT

Objectives: Acute lymphoblastic leukemia (ALL) treatment is changing rapidly as immunotherapy, targeted drugs, and measurable residual disease (MRD) testing move into routine care. This review summarizes major therapeutic advances reported between 2019 and 2026.

Methods: This SANRA-informed narrative review synthesized peer-reviewed clinical studies, major guidelines and consensus recommendations, and regulatory sources, emphasizing evidence from January 2019 through 15 August 2026 with selective earlier landmark studies. Evidence was summarized descriptively; no formal systematic-review screening, risk-of-bias assessment, GRADE evaluation, or meta-analysis was performed.

Results: In ECOG-ACRIN E1910, adding blinatumomab to consolidation chemotherapy improved 3-year overall survival in adults with MRD-negative remission from 68% to 85% [33]. Preliminary conference-reported phase III GIMEMA ALL2820 results favored ponatinib plus blinatumomab over imatinib plus chemotherapy for complete hematologic remission, day-133 MRD response, and 18-month event-free survival in newly diagnosed Ph+ ALL [69]. CD19-directed CAR T-cell therapies produce high remission rates in R/R B-cell precursor ALL [35, 43, 46], while revumenib provides a targeted option for R/R KMT2A-translocated acute leukemia [22, 56]. MRD increasingly informs risk-adapted treatment decisions [66].

Conclusions: ALL treatment is becoming more personalized and increasingly guided by immunotherapy, molecular targets, and MRD, although resistance, immune toxicity, transplantation decisions, cost, and unequal access remain important barriers.

KEYWORDS

Acute Lymphoblastic Leukemia, Immunotherapy, Bispecific Antibodies, Chimeric Antigen Receptor T-cell Therapy, Targeted Therapy, Measurable Residual Disease

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1. Introduction

Acute lymphoblastic leukemia (ALL) is a malignant neoplasm arising from lymphoid progenitor cells that undergo clonal expansion in the bone marrow, peripheral blood, and extramedullary sites [19]. Although ALL accounts for only a small proportion of all cancers diagnosed in adults, it is the most common malignancy of childhood, with a peak incidence at 3 to 5 years of age [19]. Approximately 6,100 new cases are estimated to be diagnosed annually in the United States (2025 estimate) [48]. The disease displays a characteristic age distribution, with the highest incidence in early childhood [20, 34].

The clinical trajectory of ALL differs dramatically by age. In children, risk-stratified multi-agent chemotherapy built on Berlin–Frankfurt–Münster-type backbones, complemented by central nervous system (CNS) prophylaxis, achieves long-term survival approaching 90% [19]. In adults, long-term survival with older intensive regimens historically remained substantially lower, at approximately 30–40%, reflecting a higher prevalence of adverse genetic subtypes, poorer tolerance of intensive therapy, and more frequent relapse [27, 34]. Although the bone marrow is the principal site of disease, overt CNS involvement may be present at diagnosis, and isolated CNS relapse remains an important failure mode across age groups, underscoring the need for effective prophylaxis within every treatment regimen [19]. Adolescents and young adults (AYA) represent a particularly vulnerable group in whom treatment outcomes vary widely depending on whether pediatric or adult protocols are applied [50].

For decades, the treatment of ALL rested on the same three pillars: remission induction, consolidation, and prolonged maintenance chemotherapy, with allogeneic hematopoietic stem cell transplantation (allo-HSCT) reserved for high-risk and relapsed disease. This paradigm began to erode when targeted, and immunotherapeutic agents demonstrated the capacity to replace or complement conventional chemotherapy.

The regulatory milestones since 2017 illustrate the pace of change. The anti-CD19 chimeric antigen receptor (CAR) T-cell product tisagenlecleucel and the anti-CD22 antibody–drug conjugate inotuzumab ozogamicin were approved in 2017, and brexucabtagene autoleucel followed for adult relapsed or refractory (R/R) B-cell precursor ALL in 2021. In 2024, the CD3×CD19 bispecific T-cell engager blinatumomab, previously approved for relapsed or refractory and MRD-positive disease, received approval for consolidation of CD19-positive, Philadelphia chromosome-negative (Ph-negative) B-cell precursor ALL; ponatinib received accelerated approval with chemotherapy for newly diagnosed Ph+ ALL; revumenib was approved for R/R acute leukemia with a KMT2A translocation; and obecabtagene autoleucel was approved in November for adult R/R B-cell precursor ALL [52–57, 62, 64].

The field is now evolving so rapidly that individual trial results can be difficult to place within a coherent treatment algorithm, particularly because several registrational trials have published mature follow-up data only recently. The objective of this narrative review is to synthesize the latest evidence published between 2019 and 2026 on novel therapeutic strategies for ALL. The review addresses five specific questions: (i) how have bispecific antibodies reshaped frontline consolidation and relapse therapy; (ii) what is the current role of CAR T-cell therapy across age groups; and (iii) how are tyrosine kinase inhibitors and emerging small molecules redefining Ph+ and KMT2A-rearranged ALL. Two further questions concern (iv) how MRD measurement has evolved from a prognostic marker into a therapeutic driver, and (v) which clinical and economic challenges remain unresolved. The remainder of this article is organized as follows: Section 2 describes the methodology of the literature review; Section 3 presents the findings in eight thematic subsections; Section 4 discusses the implications, limitations, and barriers to implementation; and Section 5 provides concluding remarks and directions for future research.

2. Methodology

The methodological reporting of this narrative review was informed by the Scale for the Assessment of Narrative Review Articles (SANRA) [5]. This was a narrative, not systematic, review. The final evidence base emphasized English-language peer-reviewed clinical studies published from 2019 through 15 August 2026, supplemented by selected earlier landmark studies and official regulatory and guideline sources needed for context. Eligible evidence included randomized trials, phase 1–3 studies, major real-world cohorts, reviews, consensus or guideline documents, and regulatory sources relevant to children or adults with B- or T-lineage ALL and the therapies considered here. Evidence was selected for direct relevance to the review of questions and synthesized descriptively by study design, population, intervention or comparator, efficacy and MRD endpoints, and safety. Because the review was not designed as a systematic review, database-specific retrieval, deduplication, and PRISMA-style screening counts are not reported. No formal study-level risk-of-bias assessment, GRADE evaluation, or meta-analysis was performed. This approach limits reproducibility and may introduce selection bias, limitations that are addressed further in Section 4.4.

3. Results

3.1 Current Standard of Care and Risk Stratification

The diagnostic and prognostic framework for ALL has been substantially revised by two contemporary classifications: the fifth edition of the World Health Organization Classification of Haematolymphoid Tumours (WHO-HAEM5) and the International Consensus Classification (ICC), both published in 2022 [1, 3]. The classifications emphasize genetically defined subtypes of B-cell precursor ALL (BCP-ALL), including B-ALL with BCR::ABL1 fusion, BCR::ABL1-like (Ph-like) ALL, KMT2A-rearranged ALL, ETV6::RUNX1-positive ALL, high hyperdiploid ALL, low hypodiploid ALL, TCF3::PBX1-positive ALL, iAMP21-positive ALL, and DUX4-, MEF2D-, and ZNF384-rearranged subtypes [1, 3]. WHO-HAEM5 retains T-ALL/LBL not otherwise specified and early T-precursor ALL/LBL, whereas the ICC additionally recognizes provisional genetically defined T-ALL subgroups, including HOXA-dysregulated disease [1, 3]. Consequently, comprehensive genetic characterization using cytogenetic and molecular methods is central to the initial work-up, with NGS increasingly used to refine subtype assignment and identify actionable lesions [1, 3, 60].

Risk stratification integrates age, presenting white blood cell count, genetic subtype, early treatment response, and MRD kinetics [36, 60]. Children are treated on risk-adapted Berlin–Frankfurt–Münster-type

protocols, whereas adults may receive pediatric-inspired or other risk-adapted regimens such as hyper-CVAD, with a tyrosine kinase inhibitor (TKI) incorporated in Ph⁺ disease [36, 61]. The GRAALL-2003 phase 2 study enrolled 225 adults aged 15–60 years and was retrospectively associated with better outcomes than the historical LALA-94 cohort, with the benefit being clearest in patients up to 45 years of age [18]. The CALGB 10403 trial enrolled 318 patients aged 17–39 years, of whom 295 were evaluable; 3-year EFS was 59% and 3-year OS was 73%, with outcomes higher than historical controls treated on adult protocols [50]. These data, together with the risk-adapted integration of novel agents described below, inform contemporary care [36, 61]. Table 1 summarizes selected FDA-approved agents discussed throughout this review.

Table 1. Selected FDA-approved therapies relevant to contemporary ALL treatments. Sources: FDA regulatory documents [52–57, 62–65] and representative trial evidence [11, 15, 22, 23, 29, 31, 33, 35, 37, 43, 46]. MRD = measurable residual disease; R/R = relapsed or refractory; BCP-ALL = B-cell precursor acute lymphoblastic leukemia; Ph = Philadelphia chromosome; CR = complete remission.

Agent	Class / target	FDA-approved indication(s)	Representative study/studies
Blinatumomab	Bispecific T-cell engager, CD19×CD3	R/R BCP-ALL; MRD-positive BCP-ALL in first or second CR with MRD $\geq 0.1\%$ (2018) [62]; consolidation of CD19-positive, Ph-negative BCP-ALL in adults and children ≥ 1 month (2024) [55]	TOWER; BLAST; E1910
Inotuzumab ozogamicin	Antibody–drug conjugate, CD22-calicheamicin	Adult R/R BCP-ALL (2017) [53]; R/R CD22-positive BCP-ALL in children ≥ 1 year (2024) [63]	INO-VATE; AALL1621
Tisagenlecleucel	CAR T-cell, CD19 (4-1BB)	B-cell precursor ALL in patients up to 25 years of age that is refractory or in second or later relapse (2017) [52]	ELIANA
Brexucabtagene autoleucel	CAR T-cell, CD19 (CD28)	Adult R/R BCP-ALL (2021) [54]	ZUMA-3
Obecabtagene autoleucel	CAR T-cell, CD19 (4-1BB, fast off-rate)	Adult R/R BCP-ALL (2024) [57]	FELIX
Revumenib	Menin inhibitor	R/R acute leukemia with KMT2A translocation in adults and pediatric patients ≥ 1 year (2024) [56]	AUGMENT-101
Ponatinib	Tyrosine kinase inhibitor, BCR:ABL1 (including T315I)	Newly diagnosed Ph ⁺ ALL in adults, combined with chemotherapy (accelerated approval, March 2024) [64]	PhALLCON
Nelarabine	Purine analogue (T-cell selective)	T-ALL and T-cell lymphoblastic lymphoma in adults and children ≥ 1 year whose disease has not responded to or has relapsed after at least two chemotherapy regimens (2005) [65]	AALL0434

3.2 Measurable Residual Disease as a Therapeutic Driver

MRD—the persistence of leukemic cells below the threshold of morphological detection—is now established as a strong and consistent prognostic factor for relapse in ALL [9, 15, 58] and serves as a key decision driver for therapy selection; recent expert recommendations standardize its clinical use, including assay selection, timing of assessments, and interpretation of results for therapeutic decision-making [66]. Three technologies are used in clinical practice: multiparameter flow cytometry with a sensitivity of approximately 10^{-4} in validated laboratories (with performance remaining panel-dependent); allele-specific oligonucleotide quantitative polymerase chain reaction (ASO-qPCR) with a sensitivity of approximately 10^{-4} to 10^{-5} ; and high-throughput NGS of immunoglobulin and T-cell receptor gene rearrangements, which can achieve sensitivities of up to 10^{-6} depending on assay design and DNA input [12, 58, 66]. MRD diagnostics have been harmonized across laboratories under the EuroMRD framework for PCR-based methods [58]. Table 2 summarizes the operational characteristics of these methods.

Table 2. Comparison of methods for measurable residual disease assessment in ALL [12, 58, 66].

ASO-qPCR = allele-specific oligonucleotide quantitative polymerase chain reaction; Ig = immunoglobulin; NGS = next-generation sequencing; TCR = T-cell receptor. Turnaround times are approximate and laboratory dependent.

Method	Sensitivity	Turnaround time	Advantages	Limitations
Multiparameter flow cytometry	Approximately 10^{-4} in validated laboratories (panel-dependent)	Rapid; laboratory-dependent	Broadly available; protocol-dependent standardization	Operator-dependent; requires fresh sample
ASO-qPCR	10^{-4} – 10^{-5}	3–4 weeks for assay design; ~1 week per follow-up sample	High sensitivity; widely validated	Patient-specific primers; applicable in ~90–95% of cases
NGS of Ig/TCR rearrangements	Up to 10^{-6} (assay- and input-dependent)	~7 days	Potential sensitivity up to 10^{-6} ; expanding clinical validation	Requires diagnostic sample and adequate DNA input; higher cost

MRD negativity is conventionally defined as a level below the detection limit of the applied assay, and assessments at protocol-defined timepoints—commonly including the end of induction and post-consolidation assessments—guide decisions such as treatment intensification, immunotherapy assignment, and transplantation [9, 58].

MRD status at the end of induction and consolidation strongly stratifies relapse risk in both children and adults [9]. The BLAST study (N = 116) demonstrated that MRD-positive patients in complete remission (CR) who received blinatumomab achieved complete MRD response in 78% of 113 evaluable patients; among 110 patients with Ph-negative ALL, the 18-month relapse-free survival estimate was 54%, and median OS was 36.5 months [15]. The randomized ECOG-ACRIN E1910 trial extended this principle to MRD-negative patients: among 224 adults aged 30–70 years with BCR:ABL1-negative BCP-ALL in MRD-negative remission after induction and intensification, four cycles of blinatumomab added to four cycles of consolidation chemotherapy improved 3-year OS from 68% to 85% (hazard ratio [HR] for death, 0.41; $p = 0.002$). Three-year relapse-free survival improved from 64% to 80% [33]. MRD negativity is now also used as an efficacy endpoint in registrational trials, most notably in the randomized PhALLCON trial of ponatinib versus imatinib in newly diagnosed Ph+ ALL, in which the MRD-negative CR rate at the end of induction served as the primary endpoint [23]. Collectively, these data establish MRD as a major prognostic biomarker that increasingly informs treatment of intensification, de-escalation, and therapeutic selection. Although MRD-negative complete remission has served as a primary endpoint in registrational studies such as PhALLCON [23], its formal surrogacy for long-term survival remains under evaluation. Beyond B-lineage disease, MRD-guided strategies are increasingly applied in T-ALL [66]. Standardized flow-cytometric approaches for T-ALL MRD have been developed to support this application [67].

3.3 Bispecific Antibodies

Blinatumomab, a bispecific T-cell engager that simultaneously binds CD3 on T cells and CD19 on leukemic blasts, represents the prototype of this class (Figure 1). Single-arm phase 2 studies and subsequent analyses established its activity in adults and children with R/R BCP-ALL, including relapse after allogeneic transplantation [49, 51, 59].

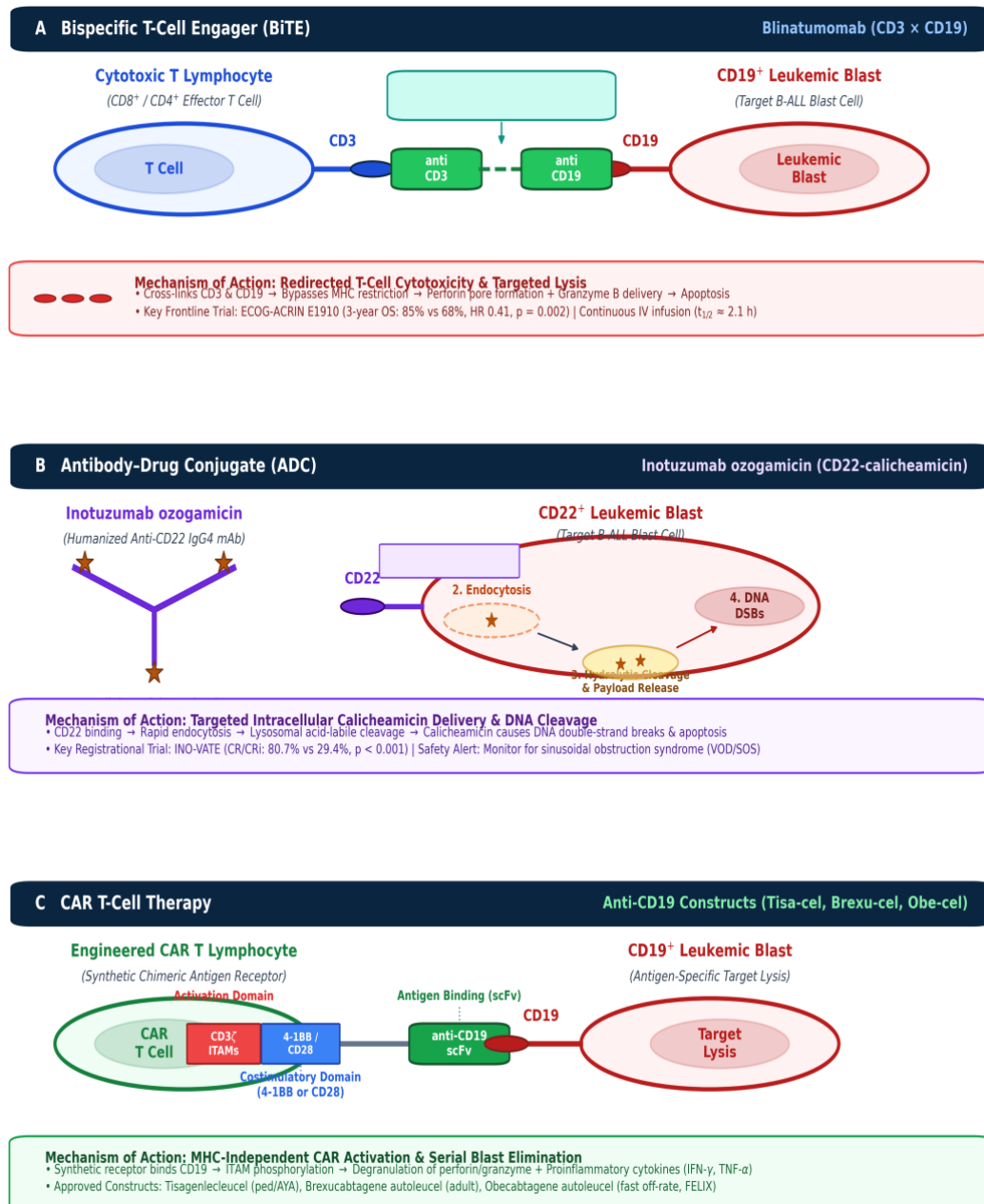


Fig. 1. Mechanisms of action of the main immunotherapeutic classes in B-cell ALL. (A) Bispecific T-cell engagers such as blinatumomab bind CD3 on T cells and CD19 on blasts, redirecting T-cell cytotoxicity against the leukemic cell. (B) Antibody–drug conjugates such as inotuzumab ozogamicin bind CD22 and deliver calicheamicin intracellularly. (C) Anti-CD19 chimeric antigen receptor (CAR) T-cells recognize and eliminate CD19-positive blasts upon antigen engagement. Figure created by the authors based on mechanistic, trial, and regulatory evidence summarized in this review [29, 31, 33, 35, 43, 46, 52, 54, 57].

In the randomized phase 3 TOWER trial (N = 405), blinatumomab produced a remission rate within 12 weeks after treatment initiation (CR with full, partial, or incomplete hematologic recovery) of 44% versus 25% with standard chemotherapy and a median OS of 7.7 versus 4.0 months in adults with R/R BCP-ALL [31]. In the MRD setting, BLAST showed an MRD response rate of 78% [15], and in pediatric first relapse the COG AALL1331 trial demonstrated that, after re-induction, blinatumomab consolidation improved 2-year OS from 58.4% to 71.3% (one-sided $p = 0.02$) and yielded numerically higher 2-year disease-free survival (54.4% versus 39.0%; one-sided $p = 0.03$, not crossing the prespecified one-sided significance threshold of 0.025) in high- and intermediate-risk patients [10]. In the parallel low-risk analysis, outcomes were not significantly different in the overall cohort, but DFS and OS improved significantly in the bone marrow $\pm$ extramedullary subgroup, with a favorable safety profile [17]. The definitive frontline evidence derives from ECOG-ACRIN E1910, which demonstrated improved survival with blinatumomab added to consolidation chemotherapy in MRD-negative adults (see Section 3.2) [33]. In 2024, the FDA approved blinatumomab for consolidation of CD19-positive, Philadelphia chromosome-negative BCP-ALL in adults and children aged 1 month and older, regardless of MRD status [55].

From a practical standpoint, blinatumomab is administered as a continuous 28-day intravenous infusion; because of the risk of early CRS and neurotoxicity, depending on the indication, treatment phase, and institutional practice, the first cycle is often delivered in hospital with step-up dosing, whereas subsequent cycles can frequently be administered on an outpatient basis [31, 33]. Expected on-target effects include B-cell aplasia and immunoglobulin depletion, which may require immunoglobulin replacement therapy [34]. A subcutaneous formulation of blinatumomab is also under evaluation; in a multicentre, single-arm, phase 1/2 trial in adults with R/R B-ALL, subcutaneous administration showed encouraging activity with a manageable safety profile [68]. In a 239-patient real-world multicenter cohort, including 227 patients treated for R/R disease, the reported response rate was approximately 65% and 47% of patients achieved MRD-negative remission [7]. Recent reviews of the immunotherapy-first approach in adults synthesize these developments and their integration into frontline algorithms [6].

3.4 Antibody–Drug Conjugates

Inotuzumab ozogamicin is a humanized anti-CD22 monoclonal antibody conjugated to the cytotoxic agent calicheamicin. In the phase 3 INO-VATE trial (N = 326), the primary CR/CRi analysis included the first 218 randomized patients (109 per arm): inotuzumab ozogamicin produced CR/CRi in 80.7% versus 29.4% with investigator's choice of chemotherapy. Among patients who achieved CR/CRi, MRD below 0.01% occurred in 78.4% versus 28.1%; in the full randomized population, median OS was 7.7 versus 6.7 months [29]. The key safety finding was a substantially higher incidence of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) of any grade: 11% versus 1% in the primary report [29] and 14.0% versus 2.1% in the final follow-up [30], particularly among patients proceeding to allo-HSCT. Contemporary practice therefore incorporates risk-mitigation strategies: fractionated dosing, avoidance of double alkylator conditioning, careful timing relative to transplantation, and vigilance for early signs of sinusoidal injury [29, 30, 36]. In clinical practice, the first inotuzumab cycle totals 1.8 mg/m², fractionated across three doses (0.8, 0.5, and 0.5 mg/m²); after CR/CRi, subsequent cycles generally total 1.5 mg/m² (0.5 mg/m² on days 1, 8, and 15) [29, 34]. In the pediatric population, inotuzumab ozogamicin demonstrated clinically meaningful activity in R/R disease in the Children's Oncology Group AALL1621 study [37]. Building on these data, the FDA approved inotuzumab ozogamicin in 2024 for pediatric patients aged 1 year and older with R/R CD22-positive BCP-ALL, based on a regulatory efficacy population of 53 patients [63]. Combinations of inotuzumab ozogamicin with chemotherapy and blinatumomab are being evaluated in frontline settings, where the risk of VOD/SOS may be more manageable because fewer patients require immediate transplantation [6, 61]. Table 3 summarizes the key trials and analyses that underpin the current treatment landscape.

Table 3. Key trials and analyses of novel therapies in acute lymphoblastic leukemia discussed in this review. Outcomes should not be directly compared across studies because of differences in populations, designs, endpoints, and follow-up. The PhALLCON MRD-negative CR percentages differ between the peer-reviewed JAMA analysis and FDA regulatory reporting despite the same endpoint-evaluable denominators (154 ponatinib; 78 imatinib); the values are therefore presented exactly as reported by each source [23, 64].

Trial	Population	Design / intervention	Key outcomes
ECOG-ACRIN E1910 [33]	Adults 30–70 y, Ph-negative BCP-ALL, MRD-negative CR1 (n = 224; 112/arm)	RCT: four cycles blinatumomab plus four cycles consolidation chemotherapy vs. four cycles consolidation chemotherapy alone	3-y OS 85% vs. 68%; RFS 80% vs. 64%
GIMEMA D-ALBA [13]	Newly diagnosed Ph+ ALL, adults (n = 63)	Phase 2: dasatinib + blinatumomab, chemo-free	Complete hematologic response 98%; 18-mo OS 95%; DFS 88%
GIMEMA immunomonitoring analysis [2]	Newly diagnosed Ph+ ALL (dasa–blina cohort, n = 43; ponatinib cohort, n = 110)	Non-randomized translational analysis of two chemo-free cohorts	Greater immune activation with dasatinib–blinatumomab
ALL2820 [69]	Newly diagnosed Ph+ ALL, adults (n = 236; 158 experimental, 78 control)	Phase 3 RCT: ponatinib plus blinatumomab vs. imatinib plus chemotherapy	CHR 94.4% vs. 79.4% (p = 0.001); day-133 MRD response 70.2% vs. 52.7% (p = 0.009); 18-mo EFS 89.9% vs. 76.8% (p = 0.011); conference abstract
PhALLCON [23, 64]	Newly diagnosed Ph+ ALL (n = 245 randomized; n = 232 endpoint-evaluable)	RCT: ponatinib plus reduced-intensity chemotherapy vs. imatinib plus reduced-intensity chemotherapy	JAMA analysis: MRD-negative CR at end of induction 34.4% vs. 16.7% (53/154 vs. 13/78); FDA analysis: 30% vs. 12% (p = 0.0004)
AALL1331 [10]	Pediatric/AYA first relapse B-ALL, high/intermediate risk	RCT: blinatumomab vs. chemotherapy post-reinduction	2-y DFS 54.4% vs. 39% (one-sided p = 0.03; not significant at the prespecified p < 0.025); 2-y OS 71.3% vs. 58.4% (one-sided p = 0.02)
TOWER [31]	Adult R/R BCP-ALL (n = 405)	RCT: blinatumomab vs. chemotherapy	Median OS 7.7 vs. 4.0 months
INO-VATE [29, 30]	Adult R/R BCP-ALL (n = 326; primary CR analysis n = 218)	RCT: inotuzumab ozogamicin vs. chemotherapy	CR/CRi 80.7% vs. 29.4%; MRD negativity among CR/CRi responders 78.4% vs. 28.1%; VOD/SOS any grade 11% vs. 1% (primary report)
ELIANA [35]	Pediatric/young adult R/R B-ALL (n = 75)	Phase 2: tisagenlecleucel	Overall remission (CR/CRi) 81%; 12-mo EFS 50%; 12-mo OS 76%
ZUMA-3 [46]	Adult R/R B-ALL (n = 55 treated; 71 enrolled)	Phase 2: brexucabtagene autoleucel	CR/CRi 71%; median OS 18.2 months
FELIX [43]	Adult R/R B-ALL (cohort 2A n = 94; infused n = 127)	Phase 1/2: obecabtagene autoleucel	Cohort 2A remission 77%; infused-patient grade ≥3 CRS 2.4%
AUGMENT-101 [21, 22]	R/R acute leukemia (mixed population: AML majority; KMT2A-r/NPM1-mutated)	Phase 1/2: revumenib	Phase 1: ORR ~53%, CR/CRh ~30% (n = 60; KMT2A-r/NPM1-mutated); phase 2: ORR 63.2%, CR/CRh 22.8% (n = 57; KMT2A-r)

Trial	Population	Design / intervention	Key outcomes
AALL0434 [11]	Newly diagnosed T-ALL, age 1–31 y (n = 1,562 evaluable; randomized comparison n = 659)	RCT: nelarabine added across postinduction therapy	5-y DFS 88.2% vs. 82.1% (nelarabine n = 323; control n = 336; p = 0.029)
CALGB 10403 [50]	AYA Ph-negative ALL (318 enrolled; 295 evaluable; age 17–39 y)	Phase 2: pediatric-inspired regimen	3-y EFS 59%; 3-y DFS 66%; 3-y OS 73%

CR/CRi = complete remission / complete remission with incomplete hematologic recovery; *CR1* = first complete remission; *CRh* = complete remission with partial hematologic recovery; *CHR* = complete hematologic remission; *CRS* = cytokine release syndrome; *DFS* = disease-free survival; *EFS* = event-free survival; *MRD* = measurable residual disease; *ORR* = overall response rate; *OS* = overall survival; *RCT* = randomized controlled trial; *RFS* = relapse-free survival; *VOD/SOS* = veno-occlusive disease/sinusoidal obstruction syndrome.

3.5 Chimeric Antigen Receptor T-Cell Therapy

Anti-CD19 CAR T-cell therapy has redefined the management of R/R BCP-ALL. Three CD19-directed CAR T-cell products are FDA-approved for BCP-ALL: tisagenlecleucel (2017) for patients up to 25 years of age with refractory disease or disease in second or later relapse, brexucabtagene autoleucel (2021) for adults with R/R BCP-ALL, and obecabtagene autoleucel (obe-cel, 2024) for adults with R/R BCP-ALL [52, 54, 57]. Obe-cel is a 4-1BB-costimulated construct with a fast off-rate CD19 binder; the FELIX program used tumor-burden-guided split dosing [24, 43].

In the registrational pediatric ELIANA trial, 75 patients received tisagenlecleucel; the overall remission rate (CR/CRi) was 81%, all responding patients achieved MRD-negative remission, and the 12-month EFS and OS were 50% and 76%, respectively [35], building on earlier single-center experiences that established the feasibility of the approach [14, 39]. In the later five-year analysis of 79 infused patients, among 70 responders, five-year RFS was 47.3% and 51.0% with and without inclusion of subsequent stem-cell transplantation in censoring, respectively; corresponding five-year OS estimates were 55.0% and 62.4%. Seventeen responders received postinfusion transplantation [16]. In adults, the phase 2 ZUMA-3 trial of brexucabtagene autoleucel reported a CR/CRi rate of 71% (39 of 55 treated patients), a median duration of remission of 12.8 months, and a median OS of 18.2 months, with grade 3 or higher CRS in 24% and grade 3 or higher neurologic events in 25% of patients [46]. The FELIX phase 1/2 trial evaluated obe-cel in 94 adults in cohort 2A and demonstrated an overall remission rate of 77% in that cohort; among 127 infused patients, grade 3 or higher CRS occurred in 2.4% and grade 3 or higher ICANS in 7.1% [43]. Tumor burden-guided split dosing contributed to this favorable toxicity profile [24]. Registry data from the Center for International Blood and Marrow Transplant Research confirm the feasibility of delivering tisagenlecleucel outside trial settings, with toxicity profiles consistent with registration studies [40]. Figure 2 summarizes selected regulatory milestones.

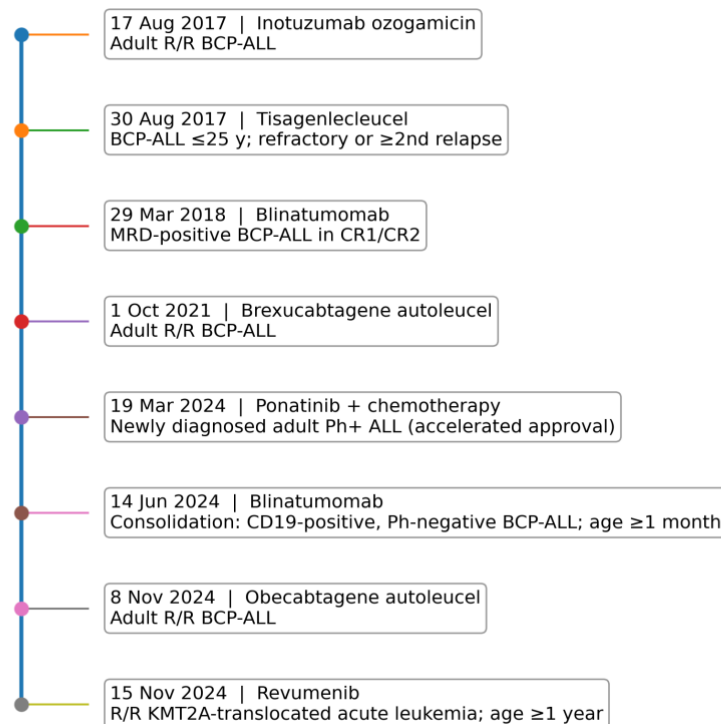


Fig. 2. Selected FDA approvals of novel therapies for acute lymphoblastic leukemia, 2017–2024 [52–57, 62, 64]. BCP-ALL = B-cell precursor acute lymphoblastic leukemia; R/R = relapsed or refractory; Ph = Philadelphia chromosome.

The principal CAR-specific toxicities are CRS and immune effector cell-associated neurotoxicity syndrome (ICANS), graded according to the American Society for Transplantation and Cellular Therapy consensus criteria [32]. For CRS, tocilizumab with or without corticosteroids is standard; moderate-to-severe ICANS is managed primarily with corticosteroids and supportive neurologic care because tocilizumab has limited efficacy against isolated neurotoxicity [32, 44, 70]. Additional challenges include B-cell aplasia with hypogammaglobulinemia, prolonged cytopenias, and a heightened risk of infections; Table 4 provides an overview of class-specific toxicities and their management. Mechanisms of resistance include CD19-negative antigen escape, documented in long-term follow-up of CD19-directed CAR therapy in adults [39], which has motivated dual-targeting and next-generation constructs, including allogeneic, off-the-shelf products [8]. Allogeneic CAR T-cell products such as UCART19 have demonstrated feasibility and antileukemic activity in early-phase trials, with remission in 14 of 21 treated patients (67%) at the day-28 assessment in combined pediatric and adult phase 1 studies [8]. These products may address manufacturing delays ('vein-to-vein' time) and improve immediate treatment availability [8]. In patients who respond to CAR T-cell therapy, post-CAR allo-HSCT remains individualized; durable remission without transplantation has been documented particularly in pediatric cohorts [16, 36, 61]. Beyond biological challenges, CAR T-cell therapy requires specialized manufacturing and delivery infrastructure, which can constrain access [6, 34, 40]. Product-specific differences, including costimulatory domain design, persistence characteristics, and bridging-chemotherapy policies, further influence the choice of construct and its applicability to individual patients [35, 43, 46].

3.6 Tyrosine Kinase Inhibitors and Philadelphia Chromosome-Positive ALL

Ph+ ALL, defined by the BCR:ABL1 fusion, accounts for approximately 20–30% of adult ALL and increases in frequency with age [60, 61]. The combination of a TKI with chemotherapy or immunotherapy is now the standard of care, and the intensity of the cytotoxic backbone has been progressively reduced [36, 61]. Ponatinib has gained an increasingly prominent role because of its potency and activity against the T315I kinase-domain mutation, a frequent cause of resistance to earlier-generation TKIs [23, 36].

The GIMEMA D-ALBA phase 2 study of the chemotherapy-free regimen of dasatinib with blinatumomab in 63 patients with newly diagnosed Ph+ ALL demonstrated a complete hematologic response rate of 98%; 60% of patients (33 of 55 evaluable) achieved a molecular response after two blinatumomab cycles, and at 18 months OS was 95% with a disease-free survival of 88% [13]. The optimal TKI in this setting remains debated: dasatinib has a favorable immunomodulatory profile that may potentiate T-cell engagers, whereas ponatinib is particularly relevant when T315I mutations are present because of its retained activity against this resistance mutation [2, 23]. A translational immunomonitoring analysis of patients treated on the two GIMEMA chemo-free platforms reported greater immune activation with dasatinib–blinatumomab, supporting the activity of both approaches [2]. In parallel, single-center series from the MD Anderson Cancer Center have shown that the combination of ponatinib with blinatumomab yields high rates of deep molecular response (complete molecular response in 87% of evaluable newly diagnosed patients; 33/38) and a low reliance on allo-HSCT [25]; at longer follow-up of the same cohort, 3-year OS was approximately 91% [28]. In a non-randomized propensity-score analysis comparing blinatumomab plus ponatinib with hyper-CVAD plus ponatinib in newly diagnosed Ph+ ALL, matched cohorts of 40 patients per arm showed significantly improved 2-year progression-free survival (91% versus 70%; $p = 0.039$) and overall survival (100% versus 78%; $p = 0.027$) in favor of the chemotherapy-free regimen, with markedly lower non-relapse mortality; this remains lower-level evidence than randomized data [45]. Additionally, a phase 2 trial of mini-hyper-CVD with blinatumomab and ponatinib has reported promising efficacy with an attenuated-intensity regimen [26]. In the randomized phase 3 PhALLCON trial, ponatinib achieved a higher MRD-negative CR rate at the end of induction than imatinib (34.4% versus 16.7%; 53/154 versus 13/78) when both were combined with reduced-intensity chemotherapy in newly diagnosed Ph+ ALL, with rare arterial occlusive events (2.5% versus 1.2%), providing the basis for frontline use of ponatinib; the FDA regulatory analysis reported an MRD-negative CR rate of 30% versus 12% (risk difference 0.18; $p = 0.0004$) [23, 64]. In a prospective phase 2 cohort of 76 patients receiving ponatinib–blinatumomab, 10 patients relapsed; $WBC \geq 70 \times 10^9/L$ at diagnosis was the only variable significantly associated with relapse on multivariable analysis, CD19 expression remained high at relapse; among four marrow relapses with reported ABL1 kinase-domain results, two harbored kinase-domain mutations [47].

The randomized phase 3 GIMEMA ALL2820 trial provided the first head-to-head comparison of a chemotherapy-free targeted/immunotherapeutic strategy with TKI-based chemotherapy in newly diagnosed adult Ph+ ALL. Among 236 patients, ponatinib plus blinatumomab produced higher CHR than imatinib plus chemotherapy (94.4% versus 79.4%; $p = 0.001$), higher day-133 MRD response (70.2% versus 52.7%; $p = 0.009$), and better 18-month EFS (89.9% versus 76.8%; $p = 0.011$) [69]. These first results were reported in a conference abstract and require confirmation with mature follow-up and peer-reviewed publication.

Ph-like (BCR:ABL1-like) ALL is a high-risk subtype identified by a gene expression profile similar to Ph+ ALL but lacking the BCR:ABL1 fusion, affecting 10–13% of children, 21% of adolescents, and 27% of young adults [42]. CRLF2 rearrangements account for approximately half of Ph-like cases, ABL-class fusions (ABL1, ABL2, CSF1R, PDGFRB) occur in approximately 13% of cases and are sensitive to dasatinib, and JAK2/EPOR rearrangements and other JAK-pathway alterations have shown sensitivity to JAK inhibitors in experimental models [42]. Timely genetic screening for Ph-like ALL is therefore clinically important, since targeted agents can be added to the backbone early in therapy; molecular fusion panels may facilitate timely identification of actionable lesions [42], and contemporary expert recommendations advise comprehensive molecular characterization at diagnosis in precisely these cases [60].

3.7 Small-Molecule Inhibitors and Emerging Agents

Beyond TKIs, several small-molecule programs are expanding the armamentarium. Venetoclax-based combination regimens have demonstrated activity in R/R ALL; in a phase 1 study of 47 heavily pretreated children and adults with ALL or lymphoblastic lymphoma, venetoclax combined with low-dose navitoclax and chemotherapy produced CR/CRi/CRp in 59.6% (28/47), including patients refractory to prior immunotherapy [41]. Combination regimens of venetoclax with chemotherapy, TKIs, and immunotherapeutic agents are under investigation, and venetoclax-based lower-intensity regimens are of particular interest for older and frail adults who tolerate intensive consolidation poorly [6, 41].

The most consequential recent advance is the menin inhibitor revumenib, which disrupts the binding of menin to KMT2A fusion proteins that drive leukemogenesis in KMT2A-rearranged leukemia—a subtype long considered high risk in both children and adults. In the phase 1 portion of the AUGMENT-101 program, revumenib produced CR/CRh (CR with partial hematologic recovery) in 30% of the efficacy analysis population with KMT2A-rearranged or NPM1-mutated acute leukemia [21]; the phase 2 registration portion subsequently confirmed activity in KMT2A-rearranged disease, with CR/CRh in 22.8% of 57 evaluable patients [22]. Based on these data, the FDA approved revumenib in November 2024 for adult and pediatric patients aged 1 year and older with R/R acute leukemia harboring a KMT2A translocation [56]. Importantly, AUGMENT-101 included a mixed population of KMT2A-translocated acute leukemias: in the regulatory efficacy population of 104 patients, 86 had AML, 16 had ALL, and 2 had mixed-phenotype acute leukemia, with an overall CR/CRh rate of 21.2%; the reported response estimates should therefore not be interpreted as ALL-specific efficacy [56]. Activity has also been confirmed in NPM1-mutated acute myeloid leukemia [4], and differentiation syndrome—a recognized on-target toxicity mediated by release of the myeloid differentiation block—occurred in a substantial proportion of patients and requires early recognition and corticosteroid management [21, 22]. Combination strategies pairing revumenib with venetoclax, hypomethylating agents, and chemotherapy are under investigation [22].

Therapeutic progress in T-ALL has been more limited than in B-lineage ALL. Nelarabine, a purine analogue with selective T-lymphoblast activity, improved 5-year disease-free survival from 82.1% to 88.2% when added to the chemotherapy backbone in the COG AALL0434 trial of newly diagnosed T-cell ALL in children and young adults [11], and it remains incorporated in contemporary management of relapsed T-ALL [36, 61]. In a single-center phase 1 study, donor-derived CD7-directed CAR T-cells produced complete remission in 90% of heavily pretreated patients (18/20); targeting CD7 can also deplete normal CD7-positive T cells and requires careful management of immune suppression [38]. An autologous CD7 CAR-T approach manufactured without healthy T-cell pre-selection has also shown feasibility, with CR/CRi in 85% of 27 infused patients at day 30 [71]. Venetoclax-based regimens are also being explored in early T-cell precursor ALL, a high-risk subtype with a traditionally poor prognosis [41, 61].

3.8 Pediatric-Inspired Regimens in Adults and the Chemotherapy-Free Vision

The progressive intensification of adult protocols toward pediatric-style schedules—higher cumulative asparaginase, vincristine, and corticosteroid doses, with prolonged maintenance—has been one of the most important chemotherapy-based advances in adult ALL over the past decade. The CALGB 10403 trial established the benchmark for pediatric-inspired therapy in adolescents and young adults [50], and pediatric-inspired backbones now form the platform onto which immunotherapeutic agents are layered. The E1910 design itself illustrates this evolution: a pediatric-inspired induction and consolidation followed by randomization to four cycles of blinatumomab plus four cycles of consolidation chemotherapy or four cycles of consolidation chemotherapy alone [33].

The emerging vision is of chemotherapy-free or chemotherapy-minimal regimens. In Ph+ ALL, the D-ALBA and subsequent GIMEMA experiences, together with the MD Anderson ponatinib-blinatumomab series, indicate that durable molecular remissions can be achieved in a substantial proportion of patients without systemic cytotoxic chemotherapy and without routine allo-HSCT [2, 13, 25]. For Ph-negative BCP-ALL, E1910 demonstrates that blinatumomab can supplement, rather than replace, consolidation chemotherapy in MRD-negative remission [33]. Trials combining blinatumomab with inotuzumab ozogamicin and reduced-intensity chemotherapy are ongoing, and it is plausible that the role of allo-HSCT will continue to contract as MRD-guided immunotherapy expands [6]. Nevertheless, unresolved questions remain: the optimal duration of maintenance after immunotherapy, the management of CNS sanctuary disease without intensive intrathecal therapy, and the extension of these principles to older adults and to T-ALL. Adaptation of immunotherapy-

first approaches for older and frail adults is likewise being evaluated, and these populations may derive particular benefit from the reduced cytotoxicity of antibody- and T-cell-based strategies [6]. From a health-economic perspective, the cost-effectiveness of chemotherapy-free strategies remains uncertain and requires formal evaluation.

Table 4 provides a consolidated overview of selected characteristic toxicities of the main therapeutic agents discussed in Sections 3.3–3.8.

Table 4. Selected characteristic toxicities of the main ALL therapies discussed in this review and their prevention and management.

Toxicity	Agents	Typical presentation	Prevention and management
Cytokine release syndrome (CRS)	Blinatumomab, CAR T-cells	Fever, hypotension, hypoxia; typically, early after exposure	Step-up dosing and early monitoring; ASTCT grading; tocilizumab ± corticosteroids; supportive care; temporary dose reduction or infusion interruption for blinatumomab according to product guidance [32, 43, 46, 70]
ICANS / neurotoxicity	Blinatumomab, CAR T-cells	Encephalopathy, aphasia, seizures	ASTCT grading; blinatumomab: dose modification or temporary infusion interruption per label; CAR T-cells: corticosteroids and supportive neurologic care according to grade; tocilizumab is not routine treatment for isolated ICANS [32, 44, 70]
VOD/SOS	Inotuzumab ozogamicin	Weight gain, ascites, hyperbilirubinemia, especially peri-transplant	Risk-adapted/fractionated dosing; minimize hepatotoxic conditioning; close monitoring around transplantation [29, 30, 34]
B-cell aplasia / hypogammaglobulinemia	CD19-directed therapies	Recurrent sinopulmonary infections, low IgG	Intravenous immunoglobulin substitution
Prolonged cytopenias / infections	CAR T-cells, blinatumomab	Neutropenia, anemia, thrombocytopenia	G-CSF according to product/institutional guidance; transfusion support; antimicrobial prophylaxis [70]
Differentiation syndrome	Revumenib (menin inhibitors)	Fever, edema, pulmonary infiltrates, leukocytosis	Corticosteroids; transient drug interruption
QT/QTc prolongation	Revumenib	Prolonged QTc on ECG monitoring	Baseline and periodic ECG/electrolyte monitoring; dose modification per product label [56]
Vascular events	Ponatinib	Arterial/venous thrombosis, hypertension	Dose optimization; cardiovascular risk management
Hepatotoxicity / pancreatitis	Asparaginase, TKIs	Elevated transaminases/bilirubin, pancreatitis	Monitoring, dose adjustment, substitution

Sources: [21–23, 29, 30, 32, 34, 43, 44, 46, 56, 70]. ASTCT = American Society for Transplantation and Cellular Therapy; ICANS = immune effector cell-associated neurotoxicity syndrome; VOD/SOS = veno-occlusive disease/sinusoidal obstruction syndrome; TKI = tyrosine kinase inhibitor.

4. Discussion

4.1 Principal Findings

The evidence synthesized in this review documents a substantial evolution of ALL therapy between 2019 and 2026. Five developments stand out. First, immunotherapy has moved into frontline treatment: in the E1910 trial, the addition of blinatumomab to consolidation chemotherapy in MRD-negative adults improved 3-year overall survival from 68% to 85%, representing a clinically substantial survival benefit [33]. Second, chemotherapy-free regimens are increasingly being investigated and adopted in selected patients with Ph+ ALL. Much of the mature supporting evidence remains phase 2 and single-center—the D-ALBA study and subsequent GIMEMA cohort analyses, together with the MD Anderson ponatinib–blinatumomab experience, show that deep, durable molecular remissions can be achieved without systemic cytotoxic chemotherapy and with a diminished role for allo-HSCT [2, 13, 25]—while preliminary randomized phase 3 ALL2820 data are now available [69]. Third, the CAR T-cell armamentarium has expanded and matured: five-year follow-up of ELIANA has demonstrated durable remissions [16], and the FELIX study reported low rates of severe CRS and ICANS with obo-cel [43]. Fourth, KMT2A-rearranged leukemia, historically one of the highest-risk subsets, is now therapeutically targetable through menin inhibition [21, 22]. Fifth, MRD has moved from a prognostic biomarker toward a therapeutic decision driver, functioning simultaneously as a trial endpoint, a factor informing therapeutic decisions, and a measure of response depth [15, 23, 33].

4.2 Comparison with Previous Knowledge

Earlier syntheses of the immunotherapy era emphasized proof of activity in R/R disease, where response rates were impressive but durability modest [29, 31]. The present review shows that the decisive progress of 2019–2026 has occurred at the intersection of three conceptual shifts: moving active agents earlier into the disease course; using immunotherapy to supplement, and in selected Ph+ regimens reduce or omit, cytotoxic components; and using MRD to allocate therapy dynamically. The E1910 design is emblematic—immunotherapy deployed as consolidation in patients already in MRD-negative remission—and the findings demonstrate that blinatumomab provides clinically meaningful benefit even in patients with conventional MRD-negative remission, potentially reflecting eradication of residual leukemic cells below the detection limits of conventional assays [33]. Preliminary head-to-head results from the phase 3 GIMEMA ALL2820 trial extend this evidence: in newly diagnosed adult Ph+ ALL, ponatinib plus blinatumomab produced higher CHR (94.4% versus 79.4%; $p = 0.001$), higher day-133 MRD response (70.2% versus 52.7%; $p = 0.009$), and better 18-month EFS (89.9% versus 76.8%; $p = 0.011$) than imatinib plus chemotherapy [69]. These conference-reported findings require confirmation in a full peer-reviewed primary publication with mature follow-up. Guidelines and reviews have progressively incorporated these principles since the MRD era, but the rapidity of data evolution means that published recommendations may lag behind contemporary evidence [6, 36, 60, 61]. Real-world cohort studies have generally reported outcomes consistent with clinical-trial evidence for blinatumomab and tisagenlecleucel [7, 40].

4.3 Remaining Barriers: Toxicity, Resistance, and Access

Despite the advances, substantial obstacles persist. Toxicity management remains resource-intensive: CRS and ICANS require specialized management, and early markers such as disease burden and T-cell expansion kinetics have been identified [32, 44]. VOD/SOS continues to complicate inotuzumab ozogamicin use, particularly around transplantation [30], and ponatinib requires cardiovascular monitoring, with arterial occlusive events reported in 2.5% of patients in PhALLCON [23]. Resistance is the second major challenge. CD19-negative antigen escape limits the durability of CD19-directed therapy [39], motivating dual-targeting and allogeneic products [8]. Molecular analyses after ponatinib–blinatumomab indicate that high presenting disease burden, particularly $WBC \geq 70 \times 10^9/L$, is the dominant relapse predictor; CD19 expression remained high at relapse, and ABL1 kinase-domain mutations were not uniformly present among marrow relapses [47]. Third, access and cost present practical barriers: CAR T-cell manufacturing, product cost, and specialized delivery requirements can constrain access [6, 34, 40]. Finally, evidence remains less mature in T-ALL and in older, frail adults [6, 34, 61]. In T-ALL, the absence of a lineage-restricted surface target comparable to CD19 complicates immunotherapy. CD7-directed CAR approaches include both donor-derived and autologous

constructs, but remain constrained by on-target depletion of normal CD7-positive T cells, manufacturing complexity, and the need for further validation [38, 71]. Older adults with comorbidities tolerate intensive pediatric-inspired regimens poorly, and low-intensity immunotherapy-based combinations are therefore an important research priority for this growing population [6, 34]. With increasing numbers of long-term pediatric CAR T-cell survivors, long-term immune reconstitution and other late effects require continued surveillance [16, 35].

4.4 Limitations of This Review

This review has several limitations. It is a narrative synthesis rather than a systematic review and, in line with its design, no formal risk-of-bias appraisal, quantitative pooling, or evidence of grading (GRADE) was undertaken. Evidence selection emphasized English-language publications and was not designed to be exhaustive in the manner of a systematic review; database-specific retrieval, deduplication, and PRISMA flow counts are therefore not available. The rapidly moving regulatory landscape also means that very recent approvals or trial readouts may postdate the review for cutoff. The thematic emphasis reflects the authors' judgment, and publication bias may overrepresent positive results. Finally, some data drawn from congress presentations, particularly ALL2820, remain to be confirmed in full peer-reviewed primary publications.

4.5 Implications for Practice and Research

For clinical practice, the synthesis supports several principles: molecular subtype assignment at diagnosis is now central because it determines therapy [1, 3, 60]; MRD assessment should occur at standardized timepoints and guide escalation or de-escalation [58, 66]. Current evidence supports incorporation of blinatumomab into consolidation for appropriately selected adults with Ph-negative BCP-ALL [33]; chemotherapy-free TKI-immunotherapy regimens are an increasingly used frontline option for selected patients with Ph+ ALL [13, 25]; and for patients with R/R KMT2A-translocated acute leukemia, eligibility for menin-inhibitor therapy should be assessed in accordance with current regulatory indications and clinical guidance [22, 56]. The research agenda for the coming decade should prioritize randomized evaluation of chemo-free platforms in Ph-negative ALL; dual-targeting and allogeneic CAR constructs to overcome antigen escape and manufacturing bottlenecks; combination strategies for menin inhibitors; prevention and pre-emption of immune toxicity; treatment optimization for T-ALL and older adults; and health-economic analyses to support equitable access. As cooperative groups and regulators converge on MRD-based endpoints, the tempo of evidence generation is likely to accelerate further, with pragmatic trials increasingly informing the applicability of these advances outside specialized centers [6, 36, 61].

5. Conclusions

The treatment of acute lymphoblastic leukemia has undergone substantial change over the past decade. Between 2019 and 2026, immunotherapy has moved into frontline and consolidation strategies in selected ALL settings, measurable residual disease has become a major therapeutic decision driver, chemotherapy-free regimens have proved feasible in Philadelphia chromosome-positive disease, CAR T-cell therapy has produced durable long-term remissions with product-specific toxicity profiles, and a menin inhibitor received regulatory approval for R/R KMT2A-translocated acute leukemia. These advances have substantially expanded therapeutic options for adults, although a major outcome gap between pediatric and adult ALL remains. The convergence of pediatric and adult regimens, together with the potential for immunotherapy to reduce reliance on transplantation in selected settings, may reduce treatment-related morbidity while improving long-term survival. International collaboration in trial conduct, biomarker harmonization, and pricing and access strategies will determine how rapidly these innovations reach patients across different settings and age groups. The unresolved challenges—treatment resistance, immune toxicity, cost, and inequitable access—are formidable but well defined, and they define the agenda for the next generation of clinical trials. Future trials will determine whether fully chemotherapy-free, transplant-sparing, MRD-adaptive approaches can be safely extended to a broader proportion of patients.

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