Novel therapies for pediatric acute lymphoblastic leukemia

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Purpose of review
This review summarizes the current novel therapy landscape in pediatric acute lymphoblastic leukemia (ALL), with a focus on key clinical trials which will shape the future direction of care for these children.

Recent findings
Recent landmark immunotherapy trials in B-ALL have demonstrated significant benefit for children, adolescents, and young adults with relapsed/refractory high-risk leukemia. Due to these successes, current trials are asking the question as to whether immunotherapy can be successfully incorporated upfront. Additionally, therapies targeting novel antigens or molecular pathways are being developed, providing new options for children previously thought to have incurable leukemia.

Summary
As survival for ALL has relatively plateaued with maximizing intensity through conventional chemotherapy, continued preclinical and clinical study of novel immunotherapeutic and targeted agents is crucial to further improve outcomes in childhood leukemia.

Keywords
acute lymphoblastic leukemia, childhood leukemia, immunotherapy, targeted therapy

INTRODUCTION

Recent pediatric acute lymphoblastic leukemia (ALL) studies demonstrate 5-year survival rates exceeding 90% [1–6]. However, survival rates have recently plateaued, compelling future trials to utilize novel therapeutic approaches, as well as improve risk stratification, to further identify patients at high-risk of relapse in order to deliver more effective therapies. Additionally, outcomes in relapsed/refractory (R/R) ALL remain dismal, with survival rates around 50% in B-ALL and often <20% in T-ALL [7,8]. This review summarizes the current treatment paradigm for pediatric ALL before highlighting some of the recent groundbreaking advances in novel therapies for children, adolescents, and young adults with ALL.

Clinical introduction to acute lymphoblastic leukemia

B-cell ALL (B-ALL) is the most common form of childhood leukemia. B-ALL development is driven by 3 primary initiating genetic alterations: chromosomal aneuploidy, rearrangements that deregulate oncogene or encode chimeric transcription factors, and/or point mutations [9]. Deeper understanding of these events, as well as the unique surface proteins found on B-ALL cells, allow for the development of novel targeted and immunotherapies.

Therapy regimens for patients with newly diagnosed acute lymphoblastic leukemia

Treatment of newly diagnosed ALL consists of three phases: remission induction, consolidation, and maintenance therapy. Total treatment duration frequently lasts between 2 and 3 years for boys and girls. Remission induction phases for standard-risk patients consist primarily of three medications: glucocorticoid (prednisone or dexamethasone), vincristine, and asparaginase. For high-risk patients and patients with T-ALL, anthracyclines are added to

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KEY POINTS

- Immunotherapy is now considered a part of the standard-of-care for children with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL), now being studied as an addition to upfront therapy in high-risk patient populations such as infantile ALL.
- Targeted therapies such as apoptosis promoting and molecularly driven therapies have demonstrated activity in B-ALL, and these agents represent promise especially for patients who have failed or lack the antigens necessary for immunotherapy.
- Novel therapies have improved outcomes in T-ALL, and new reports of successful chimeric antigen receptor T-cells for T-ALL is creating hope for a disease which is highly chemotherapy refractory after disease relapse.

remission induction therapy (daunorubicin). Complete remission (CR) rates approach 98% with this induction strategy. Consolidation therapy typically consists of vincristine and mercaptopurine (standard risk patients) or cyclophosphamide, cytarabine, and mercaptopurine (high risk patients) treated on a modified Berlin–Frankfurt–Münster (BFM) backbone. Methotrexate is given during interim maintenance, either as high dose (5 g/m^2) together with vincristine and mercaptopurine, or as escalating intermediate doses of methotrexate (100–300 mg/m^2) followed by asparaginase (Capizzi methotrexate). Interim maintenance is followed by a delayed intensification phase, using similar medications as the remission induction and consolidation phases of therapy. The maintenance phase of therapy lasts nearly 2 years (B-ALL) or 3 years (T-ALL) and consists of daily mercaptopurine, weekly methotrexate, and is typically associated with every 3-month (B-ALL) or monthly (T-ALL) vincristine infusions and 5-day pulses of steroids.

Targeted therapy in pediatric B-ALL was first developed in patients with Philadelphia chromosome (translocation of *BCR-ABL1*) by use of an *ABL1* tyrosine kinase inhibitor (TKI) [10]. The addition of a TKI (imatinib mesylate) to intensive chemotherapy resulted in outcomes similar to patients who received hematopoietic stem cell transplantation (HSCT) [11]. In addition, targeted therapies interfering with the *JAK-STAT* pathway, such us the *JAK* inhibitor ruxolitinib, have recently been tested in pediatric patients with Ph-like ALL (AALL1521, NCT02723994) [12]. The initial success of these targeted therapy trials have paved the way for other novel therapies currently being used and tested in pediatric ALL. Notable examples are reviewed below.

Novel therapy approaches to target B-cell acute lymphoblastic leukemia

Immunotherapy for B-cell acute lymphoblastic leukaemia

Immunotherapy used in ALL treatment is frequently antibody or T-cell based therapy. Blinatumomab is a CD3/CD19 bispecific T-cell engager (BiTE) designed to link CD19 expressing B-cells with CD3 T-cells, causing T-cell activation and cytotoxicity. A phase 3 clinical trial conducted by the Children's Oncology Group (COG) (AALL1331, NCT02101853) enrolled patients aged 1–30 years with intermediate or high-risk B-ALL in first relapse to receive either 2 cycles of blinatumomab or 2 cycles of multiagent chemotherapy followed by HSCT. This study was terminated early by the data and safety monitoring committee (DSMC) given superiority of the blinatumomab arm of therapy with 2-year disease free survival (DFS) of 54.4% in the blinatumomab arm vs. 39.0% in the chemotherapy arm ($P = 0.03$) and 2-year overall survival (OS) of 71.3% vs. 58.4% ($P = 0.02$), respectively [13▪▪]. Blinatumomab also demonstrated a tolerable safety profile, with decreased rates of febrile neutropenia and sepsis compared to multiagent chemotherapy. Additionally, there were low rates of cytokine release syndrome (CRS) and neurotoxicity reported on this study, two unique toxicities attributed to blinatumomab. Similarly, a pediatric European study (NCT02393859) investigating blinatumomab versus consolidative chemotherapy prior to transplant confirmed superior response rates and survival with blinatumomab [14].

Given the tolerability and encouraging responses seen with blinatumomab, frontline pediatric B-ALL studies have begun incorporating blinatumomab into treatment regimens in both standard-risk children and infants. Infantile B-ALL is considered one of the most difficult-to-cure leukemias, with long-term event-free survival (EFS) around 36% in the majority of patients with *KMT2A* rearrangements [15,16]. A recent practice-changing study (NL59901.078.17, EudraCT2016-004674-17) implementing blinatumomab in upfront infantile B-ALL therapy demonstrated remarkable results, with an estimated 2-year EFS of 81.6% (compared to 49.4% in the Interfant-06 trial as a historical control) [17▪▪]. Two-year OS was 93.3% compared to 65.8% in Interfant-06 [17▪▪]. This dramatic improvement for an incredibly high at-risk population ably illuminates the potential of proper incorporation of novel therapeutics into routine therapy. Similarly, the current Children's Oncology Group Phase III trial AALL1731 (NCT03914625) is investigating the addition of blinatumomab in newly diagnosed, standard-risk B-ALL patients. This study is

ongoing, and its results will be highly anticipated, with the potential to change the standard of care in newly diagnosed pediatric B-ALL. Early adult data has generated considerable excitement for blinatumomab use in newly diagnosed B-ALL (ECOG-ACRIN E1910, NCT02003222) [18]. Studies incorporating blinatumomab in novel ways continues to be explored, with active studies listed in Table 1.

In contrast to the antibody-based therapy in blinatumomab, cellular therapy involves genetic engineering of the patient's immune cells to target leukemia. The most promising and tested cellular therapy is that of chimeric antigen receptor T-cells (CAR-T). This 'living drug' is produced by transducing a patient's T-cell lymphocytes *ex-vivo* with an antibody-derived synthetic receptor coupled with T-cell receptor co-stimulatory domains (CD28 or 4-1BB), activating these cells, and then re-infusing the final product back into the patient. Tisagenlecleucel (Kymriah) is an anti-CD19 CAR-T [19]. The Phase II ELIANA trial studying tisagenlecleucel resulted in an overall remission rate (ORR) of 81% in pediatric and young adult patients with relapsed and refractory (R/R) B-ALL [19,20▪▪]. Sustained responses were seen, with 59% of patient's leukemia free at 12-months [20▪▪]. These remarkable results led to the first Food and Drug Administration (FDA) approval of CAR-T for pediatric and young adults patients with ALL in 2017. This first in children FDA approval was a remarkable achievement for the field of cellular therapy and pediatric oncology, indicating that novel therapies can be developed with children in mind, rather than repurposing therapies previously tested and approved in adults.

Although the ELIANA trial of tisagenlecleucel demonstrated remarkable responses with single antigen targeting CAR-T, the fact that roughly half of these patients would have their leukemia eventually return demonstrated the continued need to advance the field. Antigen down regulation (via decreased CD19 expression) and antigen loss has been shown to be a major cause of relapse after CAR-T. This has resulted in the emergence of targeting novel and dual targeting of surface antigens to mitigate this problem. A phase 1 study (NCT02315612) at the National Cancer Institute established for the first time that anti-CD22 directed CAR-T could result in complete remissions in disease previously resistant to anti-CD19 directed CAR-T [21]. The AMELIA trial from the UK demonstrated safety in dual targeting with a CD19/CD22 CAR-T; however, poor persistence of the cells failed to create sustained remissions in these patients [22]. In contrast to a single CAR-T with dual targeting, studies have also included co-administration of both CD19 and CD22 directed CAR-T in R/R B-ALL patients. One such study demonstrated a stunning CR rate of 99.0%, with all patients becoming minimal residual disease (MRD) negative, and a 12-month EFS of 73.5% [23▪]. Similar to the co-administration of conventional chemotherapy with different mechanisms of action, immunotherapy targeting novel and multiple antigens simultaneously is likely to be the direction of future commercially available cellular therapies, and this area of interest is currently being tested preclinically and in ongoing clinical trials (Table 1) [24,25].

Antibody drug conjugates (ADC) couple an antibody targeting a cell surface receptor with a cytotoxic pharmaceutical payload. When the antibody binds the unique receptor to ALL cells, the ADC is internalized, releasing the payload. Inotuzmab ozogamicin (InO) is an ADC in which a monoclonal antibody targeting CD22 is coupled with a cytotoxic calicheamicin antitumor antibiotic by an acid labile linker. After binding, the molecule is internalized, releasing calicheamicin causing DNA breaks and apoptosis [26]. A phase 2 study (ITCC-059, EudraCT2016-00227-71) evaluating responses of single agent InO in R/R B-ALL patients demonstrated an ORR of 81.5%, with 81.8% of this population being MRD negative [27]. One-year EFS was 36.7% and OS was 55.1%. A similar study from the COG (AALL1621, NCT02981628) evaluated heavily pretreated R/R B-ALL patients treated with single agent InO, noting an ORR of 58.3% [28]. This single agent activity was very promising, prompting the inclusion of InO in the current COG phase III trial AALL1732 for high-risk $CD22^{+}$ B-ALL patients (NCT03959085). After an initial safety phase in AALL1732 identified increased rates of sinusoidal obstruction syndrome (SOS) (characterized by right upper quadrant pain, hepatomegaly, ascites, and thrombocytopenia), the dose of InO was decreased and antimicrobial prophylaxis was required during delayed intensification where increased rates of bacterial infections were reported. Unfortunately, ongoing concerns of increased rates of SOS during the 2nd safety phase have prompted further protocol changes [29]. The study is currently being amended, with the aim to continue to utilize this therapy in a manner that both ensures safety but also enables the efficacy demonstrated thus far.

Targeted therapy for B-cell acute lymphoblastic leukemia

Although treatment advances over the last decade in immunotherapy have changed the treatment paradigm for R/R B-ALL, novel targeted therapies have also garnered considerable excitement. Venetoclax, a *BCL-2* inhibitor, acts by inhibiting pro-survival proteins within the intrinsic apoptosis pathway, thus activating pro-apoptotic proteins and

Table 1. Current active trials using novel therapies for pediatric patients with acute lymphoblastic leukemia

Title	Registration number	Eligible ages	Sponsor
Blinatumomab Bridging therapy	NCT04556084	0–25 years	Medical College of Wisconsin
Blinatumomab after TCR alpha Beta/CD19 depleted HCT	NCT04746209	0–25 years	Medical College of Wisconsin
Study of pedi-cRIB: mini-hyper-CVD with condensed rituximab, inotuzumab ozogamicin and blinatumomab (cRIB) for relapsed therapy for pediatric with B-cell lineage acute lymphocytic leukemia	NCT05645718	1–25 years	MD Anderson Cancer Center
UCD19 CarT in treatment of pediatric B-ALL and B-NHL	NCT04544592	0–25 years	University of Colorado
A study to evaluate the safety and efficacy of JCAR017 in pediatric subjects with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL) and B-cell non-Hodgkin lymphoma (B-NHL)	NCT03743246	0–25 years	Celgene
A second infusion (early reinfusion) of tisagenlecleucel in children and young adults with B-cell acute lymphoblastic leukemia(B-ALL)	NCT05460533	0–25 years	Memorial Sloan Kettering Cancer Center
CD19/CD22 bicistronic chimeric antigen receptor (CAR) T cells in children and young adults with recurrent or refractory CD19/CD22-expressing B cell malignancies	NCT05442515	3–35 years	National Cancer Institute
CAR-20/19-T cells in patients with relapsed/refractory B cell ALL (CAR-20/19-T)	NCT04049383	1–70 years	Medical College of Wisconsin
Co-administration of CART22–65s and huCART19 for B-ALL	NCT05674175	0–29 years	University of Pennsylvania
Phase I dose escalation study of CD19/CD22 chimeric antigen receptor (CAR) T cells in children and young adults with recurrent or refractory B cell malignancies	NCT03241940	1–30 years	Stanford University
Inotuzumab ozogamicin for children with MRD positive $CD22^{+}$ lymphoblastic leukemia	NCT03913559	0–21 years	St. Jude Children's Research Hospital
Inotuzumab ozogamicin in treating younger patients with B-lymphoblastic lymphoma or relapsed or refractory CD22 positive B acute lymphoblastic leukemia	NCT02981628	1–21 years	Children's Oncology Group
Trial treating relapsed acute lymphoblastic leukemia with venetoclax and navitoclax	NCT05192889	4–30 years	St. Jude Children's Research Hospital
A study of SNDX-5613 in R/R leukemias including those with an MLLr/ KMT2A gene rearrangement or NPM1 mutation (AUGMENT-101)	NCT04065399	≥1 month	Syndax Pharmaceuticals
A study of SNDX-5613 in combination with chemotherapy in participants with leukemia	NCT05326516	≥1 month	Syndax Pharmaceuticals
PO ixazomib in combination with chemotherapy for childhood relapsed or refractory acute lymphoblastic leukemia and lymphoblastic lymphoma	NCT03817320	1–21 years	Therapeutic Advances in Childhood Leukemia Consortium (TACL)
Study of carfilzomib in combination with induction chemotherapy in children with relapsed or refractory acute lymphoblastic leukemia	NCT02303821	0–21 years	Amgen / TACL
Palbociclib in combination with chemotherapy in pediatric patients with relapsed or refractory acute lymphoblastic leukemia (RELPALL2)	NCT04996160	0–25 years	Stanford University
Phase I trial of Turalio(R) (pexidartinib, PLX3397) in children and young adults with refractory leukemias and refractory solid tumors including neurofibromatosis type 1 (NF1) Associated plexiform neurofibromas (PN)	NCT02390752	3–35 years	National Cancer Institute
Combination chemotherapy and nelarabine in treating patients with T-cell acute lymphoblastic leukemia or lymphoblastic lymphoma	NCT00501826	All ages	MD Anderson Cancer Center
Phase II study to evaluate safety and efficacy of CB-103 with venetoclax in adolescent and young adult patients with relapsed/refractory T-ALL or T-LBL	NCT05464836	12–40 years	MD Anderson Cancer Center
A phase 1/2 study of the safety and efficacy of anti-CD7 allogeneic CAR-T cells (WU-CART-007) in patients with relapsed or refractory T-ALL/LBL	NCT04984356	≥12 years	Wugen Inc.

ALL, acute lymphoblastic leukemia.

triggering permeabilization of the outer mitochondrial membrane [30]. Although venetoclax has received FDA approval in acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL), its clinical use in ALL is under current investigation. One combined pediatric/adult relapsed ALL study (NCT03181126) demonstrated safety and strong response rates combining venetoclax with low-dose navitoclax (*BCL-X$_L$/BCL-2* inhibitor) and conventional chemotherapy [31▪]. This study demonstrated a CR rate of 75% in pediatric patients, with 67% of these patients becoming MRD negative. Importantly, this chemotherapy allowed 30% of patients to be successfully bridged to HSCT or CAR-T therapy. Further inquiry is likely to define subsets of ALL patients dependent on *BCL-2* and potentially susceptible to venetoclax, including hypodiploid, *KMT2A*-rearranged (*KMT2A-r*), and *TCF3-HLF* (t(17;19)) mutated patients [32–35].

Currently, there are no targeted therapies approved for *KMT2A* rearranged (*KMT2A-r*) ALL. This genetic aberration is present in approximately 80% of infantile ALL and is seen with relative frequency in older childhood/adolescent B-ALL, mixed phenotype acute leukemia, and AML, and is typically associated with a poor prognosis [15,36]. For patients with *KMT2A-r*, Menin acts as an oncogenic cofactor, binding to the *Hox* gene promoter. Revumenib (SNDX-5613) selectively inhibits the Menin–*KMT2A* interaction [37▪▪]. The phase 1 clinical trial, NCT04065399, demonstrated an impressive CR rate of 30% in heavily pretreated R/R leukemia patients [37▪▪]. Although most patients in this trial had R/R AML, the oncology community is waiting with anticipation to review the clinical implications of having a targeted agent for the high-risk population of *KMT2A-r* B-ALL, with the Augment 101 (NCT04065399) and Augment 102 (NCT05326516) studies nearing study completion (Table 1).

Novel therapy approaches to target T-cell acute lymphoblastic leukemia

Historically, T-ALL has been more difficult to treat that B-ALL, with advances in T- ALL therapy lagging B-ALL. With recent successes in large clinical trials and new therapies on the horizon, there is new hope on the horizon.

The COG recently reported the beneficial results of adding nelarabine to an augmented BFM backbone for T-ALL [38]. Overall survival was 88.2% $\pm$2.4% at 5 years for those randomly assigned to receive nelarabine, superior to those who did not. The combination of escalating dose (Capizzi) methotrexate and nelarabine was the most successful arm of that study with 91% DFS at 5-years [38]. A further analysis demonstrated that the patients with the presence of significant amount of central nervous system (CNS) leukemia (CNS-3) experienced incredible benefit with 4-year DFS of 93.1% $\pm$5.2% for those receiving nelarabine, far exceeding the 70.2 $\pm$ 5.8% DFS for those who did not [39▪]. Of additional benefit for patients with CNS disease, the COG also recently reported that the omission of cranial radiation therapy (CRT) was safe for most patients with T-ALL given the CNS therapy improvements incorporated in systemic treatment regimens [40▪]. This has led to optimism that incorporation of nelarabine with modern systemic therapy may be sufficient to enable avoidance of CRT, and its well established deleterious long term adverse effects, in nearly all newly diagnosed T-ALL patients.

Despite the improvements in treatment regimens, relapsed T-ALL continues to be a devastating disease with extremely poor outcomes [41]. Thus, investigation of many novel therapeutics is underway (Table 1). Among the most promising options is daratumomab, a monoclonal antibody directed against the CD38 antigen found on T-cells. Effective in preclinical trials, daratumomab was studied in relapsed T-ALL patients in a phase two study (NCT03384654) and found to be both safe and improve outcomes [42–44]. This initial promise should stimulate further incorporation of daratumomab into larger clinical trials.

Immunotherapeutics in T-ALL have lagged behind the successes in B-ALL, but nascent work provides optimism for what is to come. Identification of a targetable surface antigen has limited CART options for T-ALL. Yet, a few teams have begun attempts to target the surface antigen CD7 on T-lymphoblasts. An interim analysis of a trial using base edited CART cells targeting CD7 demonstrated potential safety in such an approach, perhaps discovering an entirely new frontier of therapy options by utilizing CRISPR (clustered regularly interspaced short palindromic repeats) technology [45▪]. Additional investigations of CD7 targeted CART cells are ongoing (NCT03690011).

As T-ALL is associated with recurrent mutations in functional molecular pathways, work is underway to identify effective targets and therapeutics in many of those pathways. These investigations may lead to additional mechanisms of therapy including targeting *NOTCH* signaling, the *JAK/STAT* pathway, the *Mapk/RAS* pathway, the *mTOR* pathway and others (NCT03690011, NCT03705507, NCT01523977) [46].

CONCLUSION

Despite decades of success in improving outcomes for children with ALL, further advancement is

necessary to better achieve the goal of optimizing outcomes while minimizing toxicities. Novel therapies first developed and approved for pediatric B-ALL have paved the way for a new era in childhood cancer treatment by approaching that laudable goal. With so many exciting options emerging, it can be difficult for the healthcare provider, unaccustomed to such a landscape of choice, to know how best to optimize the sequencing and cadence of these treatments. Yet, as experience with these agents grows and further studies enable direct comparisons of these new agents, we hope to soon get clarity on the optimal timing and use of these exciting agents. We must not become complacent in searching for cures for the patients whose leukemia cannot be cured with our current technology.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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This is the first publication demonstrating safety and preliminary activity of the menin inhibitor revumenib. KMT2a-rearranged patients (such as most infants and some older children with B-ALL) often have poor outcomes, and the potential to salvage these patients (or target with upfront therapy) with a molecularly driven therapy could potentially alter therapy in ways that TKIs such as imatinib and dasatinib have altered therapy for Philadelphia-positive B-ALL.

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This study describes outcomes of T-ALL based on treatment and CNS status based on two large phase 3 clinical trials. Nelarabine has become the standard of care for T-ALL given the reduction of CNS relapses, while more studies are needed to answer other questions such as intensifying steroid use and the optimal use of cranial irradiation.

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While patients with T-lymphoblastic lymphoma benefited from bortezomib inclusion, surprisingly, patients with T-ALL did not. Bortezomib is not likely to be used in future upfront T-ALL trials as part of the standard of care.

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