

# Relapsed childhood T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma

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**Received:** September 29, 2024.

**Accepted:** December 31, 2024.

**Early view:** January 9, 2025.

<https://doi.org/10.3324/haematol.2024.285643>

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## Abstract

While outcomes for pediatric acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) have improved dramatically in recent decades, relapsed and refractory disease remain a significant therapeutic challenge. This is particularly true for patients with T-cell ALL and LBL, where survival for patients with relapsed/refractory disease remains dismal. Recent efforts to comprehensively profile the genomics of T-ALL/LBL to improve understanding of disease biology have enhanced our ability to identify high-risk patients at diagnosis who are more likely to relapse and have also identified novel targets for precision medicines. Novel immunotherapies have transformed the treatment landscape for patients with B-cell ALL (B-ALL). Many immunotherapies are under investigation in clinical trials for patients with T-ALL/LBL and early results are very promising. Given these insights into disease biology and the development of targeted and immune-based treatments, it is reasonable to hope for improved patient outcomes, although challenges remain. In this review, we summarize the present state of understanding of the risk factors for relapse of T-ALL/LBL, established treatment regimens, and the promising small molecule inhibitors and immunotherapies with the potential to revolutionize the treatment of relapsed/refractory T-ALL/LBL.

## Introduction

T-cell acute lymphoblastic leukemia (T-ALL) and lymphoblastic lymphoma (T-LBL) are rare diseases with a yearly incidence of approximately 5–6 new cases per million people aged <20 years in the United States.<sup>1</sup> T-ALL accounts for approximately 15% of pediatric ALL and T-LBL accounts for approximately 30% of pediatric non-Hodgkin lymphoma.<sup>2</sup> Over the past few decades, a succession of multi-institutional trials orchestrated largely by cooperative groups have resulted in the creation of risk-stratified multi-agent therapies able to achieve long-term overall survival (OS) rates approaching 90% for newly diagnosed children and adolescent and young adults (AYA) with T-ALL and T-LBL.<sup>3</sup> Historically, patients with relapsed and refractory (r/r) disease have had a dismal prognosis. While outcomes for B-cell ALL have improved significantly in recent years, the outcomes for r/r T-ALL/T-LBL have remained poor, with OS <30%.<sup>4</sup> A major improvement in the treatment of B-ALL has been the advent of immunotherapy, including monoclonal antibodies, bispecific antibodies, and cell therapies. Unfortunately, the

translation of immunotherapies for patients with T-ALL has been less robust. Nevertheless, several promising immunotherapies are currently in clinical trials with promising early results, raising hopes that the next decade will see similar improvements in outcome for patients with r/r T-ALL/LBL. T-cell acute lymphoblastic lymphoma is conventionally differentiated from T-ALL based on the degree of marrow involvement, using a historical cutoff of 25%. Over the past 20 years, the treatment of patients with T-ALL and T-LBL has largely been identical, as T-LBL patients were shown to have improved outcomes with leukemia-type regimens as compared with lymphoma-type regimens.<sup>5</sup> This has been reinforced by the World Health Organization (WHO), which classifies T-LBL as the same disease as T-ALL.<sup>5</sup> Yet, differential response to novel therapies has been seen in several recent trials, highlighting the fact that while T-ALL and T-LBL share many clinical and biologic features, they are different diseases. In this manuscript, we summarize the current understanding of T-ALL/LBL disease biology and approaches for its treatment, with particular attention on emerging therapies and the r/r population.

Risk factors for relapse

As survival is poor for T-ALL/T-LBL patients with relapsed disease, a major goal has been preventing relapse. One approach to reducing the risk of relapse is to identify patients who are more likely to relapse before they do so and treating those patients with alternative or more intensive therapy through risk-stratification. Risk-stratification often incorporates clinical and demographic features, leukemia biology, and response to therapy. Risk-stratification has been instrumental in the improvement in outcomes in B-ALL. For T-ALL, however, few features have been identified that can accurately risk-stratify patients independent of treatment response. Moreover, while individual cooperative groups have identified potential biomarkers that are prognostic independent of treatment response, these biomarkers have not been validated in independent studies. Our group and others recently performed integrated genomic analyses in larger cohorts of patients with more robust sequencing technologies, allowing us to identify prognostic biomarkers that may be translatable into the clinic in the near future.<sup>6</sup>

Clinical and demographic factors

The only clinical features found to be independently prognostic of treatment response in T-ALL are age and central nervous system (CNS) involvement at diagnosis. While very rare, infants <1 year of age have inferior outcomes in T-ALL, similar to B-ALL.<sup>7</sup> Older adults also have inferior outcomes.<sup>8</sup> However, recent Children’s Oncology Group (COG) phase III studies, AALL0434 and AALL1231, found T-ALL patients aged 1-30 years have similar outcomes.<sup>9</sup> This is in stark contrast to B-ALL where AYA patients fare worse than younger children. Presence of blasts in the CNS is associated with worse outcomes; however, the degree of involvement that associates with outcome depends on the treatment regimen and techniques used to identify leukemic blasts. Multiple studies have demonstrated patients with CNS3 disease have inferior outcomes. (Definitions of CNS status are detailed in Table 1.) However, patients with CNS2 had similar outcomes to those with no CNS involvement (CNS1) when treated on AALL0434/AALL1231. In contrast, patients with CNS2 had

inferior outcomes to CNS1 on UKALL2003 and UKALL2011.<sup>10,11</sup> White blood cell (WBC) count in peripheral blood at diagnosis correlates with outcome in T-ALL; however, unlike B-ALL, the prognostic significance of WBC is mitigated when considering treatment response, and many groups no longer use WBC count at presentation for risk-stratification for T-ALL.<sup>12</sup> Recent evidence shows that very high WBC counts, for example WBC >100x10<sup>9</sup>/L, or >200x10<sup>9</sup>/L for non-early T-cell precursor (non-ETP) T-ALL, may be predictive of worse outcomes.<sup>13</sup> T-cell acute lymphoblastic leukemia is twice as common in males as females, likely due to the presence of several genes on the X-chromosome being involved in leukemogenesis;<sup>2,14</sup> however, outcomes for males and females are similar. T-ALL is more prevalent in patients who self-identify as Black or African American; however, outcomes are not worse for the patients who self-identify as Black or African American or Hispanic patients compared to patients who self-identify as White.<sup>15</sup> This is also in contrast to B-ALL, where patients who self-identify as White have better outcomes.<sup>16</sup> T-cell acute lymphoblastic lymphoma is rarer than T-ALL, and so it is less clear which if any clinical and demographic features, aside from CNS status, are prognostic independent of treatment response in T-LBL. Disease involvement in bone marrow or peripheral blood at diagnosis, referred to as minimal disseminated disease (MDD), has been used in risk-stratification by some groups. In evaluating a relatively large number of pediatric patients with T-LBL treated on the prednisone reference arm of EURO-LB02, MDD >1% had no prognostic significance; however, surprisingly MDD <0.1% was associated with unfavorable outcomes compared with MDD ≥0.1%, specifically in disease without *NOTCH1* and/or *FBXW7* mutation (5-year event-free survival [EFS] 94% vs. 38%).<sup>17</sup> MDD has not been found to be prognostic by other groups on recent trials, possibly due to differences in therapy intensity.<sup>18</sup>

Response factors

Response to therapy is the only factor that is consistently identified as prognostic across trials for patients with T-ALL/LBL.<sup>13</sup> The Berlin-Frankfurt-Munster (BFM) cooperative group

Table 1. Central nervous system disease classification.\*

CNS disease	Blasts (Y/N)	RBC (1/μL)	WBC (1/μL)	$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2 \frac{\text{Blood WBC}}{\text{Blood RBC}}$ (Y/N/NA)
1	N	Any	Any	NA
2a	Y	<10	<5	NA
2b	Y	≥10	<5	NA
2c	Y	≥10	≥5	N
3a	Y	<10	≥5	NA
3b	Y	≥10	≥5	Y
3c	Symptomatic CNS involvement			

CNS: central nervous system; CSF: cerebrospinal fluid; N: no; NA: not applicable; RBC: red blood cell; WBC: white blood cell; Y: yes. \*Some cooperative groups combine patients with traumatic lumbar puncture into a single group, e.g., the approximate equivalent of CNS 2b, 2c and 3b.

utilizes a regimen that starts therapy with a one-week course of prednisone, and reduction in disease burden at the end of this prednisone pre-phase is used for risk-stratification: patients with a peripheral blood blast count of  $<1,000/\mu\text{L}$  are classified as prednisone good responders (PGR), differentiating them from prednisone poor responders (PPR). The PGR group has lower rates of relapse and improved OS compared to PPR.<sup>19</sup>

On the COG AALL0434 trial, flow cytometry-based measurable residual disease (also called minimal residual disease [MRD]) in peripheral blood after one week of induction therapy was prognostic by univariate, but not multivariate, analysis when integrated with bone marrow MRD at end of induction (EOI).<sup>13</sup> Bone marrow MRD at the end of consolidation (EOC), also called IB by some cooperative groups, is the best predictor of outcomes in T-ALL. Multiple studies have shown that patients who are MRD-positive ( $\geq 0.1\%$ ) at end of consolidation have a very poor prognosis, requiring hematopoietic stem cell transplantation (HSCT) for cure. Only a small minority of patients have persistent disease at EOC<sup>13,20</sup> and EOI MRD remains the major factor used in risk-stratification. While most patients who are MRD  $<0.01\%$  at EOI have favorable prognosis, a significant percentage of relapses do occur in these patients. More recently, methodologies with increased sensitivity in measuring MRD are being used in the clinic, such as next-generation sequencing. This will likely increase detection of residual disease and therefore increase the fraction of patients who have detectable disease at EOC. Whether this information is useful for prognostication will need to be determined in future trials. For T-LBL, response to therapy in the form of EOI MRD has been found to be prognostic as well, using a cutoff of 0.1%. It is interesting to note that while EOI MRD is prognostic, and therefore useful in risk-stratification in T-LBL, changes in disease as seen by imaging in response to therapy is not as predictive of outcome.<sup>18</sup>

### Immunophenotypic factors

The European Group for the Immunologic Classification of Leukemia (EGIL) divided T-ALL into groups based on the corresponding stage of thymocyte differentiation as defined by various cytoplasmic and surface markers:

- pro-T (CD1a<sup>-</sup>, CD2<sup>+</sup>, cytoplasmic (c)CD3<sup>+</sup>, surface (s)CD3<sup>-</sup>, CD5<sup>-</sup>, CD7<sup>+</sup>, CD34<sup>+</sup>)
- pre-T (CD1a<sup>-</sup>, CD2<sup>+</sup>, cCD3<sup>+</sup>, sCD3<sup>-</sup>, CD5<sup>+</sup>, CD7<sup>+</sup>, CD34<sup>-</sup>)
- cortical T (CD1a<sup>+</sup>, CD2<sup>+</sup>, cCD3<sup>+</sup>, sCD3<sup>+/+</sup>, CD5<sup>+</sup>, CD7<sup>+</sup>, CD34<sup>-</sup>)
- mature T (CD1a<sup>+</sup>, CD2<sup>+</sup>, cCD3<sup>+</sup>, sCD3<sup>+</sup>, CD5<sup>+</sup>, CD7<sup>+</sup>, CD34<sup>-</sup>)

Older trials found pro- and pre-T-ALL were associated with inferior outcomes and cortical T-ALL with more favorable outcomes; however, the EGIL immunologic classification has not been found to be independently prognostic with modern response-based risk stratification and treatment.<sup>12</sup> Early T-cell precursor T-ALL (ETP-ALL) was first described in 2009 based on immunophenotypic similarities with normal early T-cell precursors, defined as expressing CD2, cCD3,

and CD7, absent CD1a and CD8, and absent or dim CD5 expression. Early studies found that patients with ETP-ALL have inferior outcome. However, recent trials found that patients with ETP immunophenotype have similar outcome to non-ETP T-ALL and near ETP ALL. Near ETP describes cases that would otherwise have the immunophenotype of ETP if not for higher CD5 expression (CD5 on  $>75\%$  of blasts).<sup>21</sup> While outcomes are similar to those with ETP, near ETP and non-ETP immunophenotypes, the type of events differ. ETP and near ETP are more likely to have slower response to therapy or refractory disease than non-ETP, likely from intrinsic corticosteroid resistance; however, that is balanced by fewer relapses.<sup>2, 13</sup>

### Genetic factors

T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma is subdivided by the WHO into two groups: ETP and not otherwise specified (NOS), i.e., non-ETP.<sup>5</sup> The International Consensus Classification (ICC) recognizes three groups, T-ALL NOS, ETP NOS, and ETP *BCL11B*-activated, and recently added 8 provisional entities, *TAL1/2*-rearranged, *TLX1*-rearranged, *TLX3*-rearranged, *HOXA*, *LMO1/2*-rearranged, *NKX2*-rearranged, *SPI1*-rearranged, and *BHLH*-other.<sup>21</sup> These classifications are based on relatively small studies and are underpowered for prognostication.<sup>6</sup> There is currently no consensus in defining subtypes, likely due to the prevalence of non-coding alterations that drive T-ALL/LBL oncogenesis.<sup>22</sup> One T-ALL risk assignment strategy originally published by the Group for Research in Adult Acute Lymphoblastic Leukemia (GRAALL) described better outcomes in cases of *NOTCH1* and/or *FBXW7* mutation without *N/K-RAS* mutation and/or *PTEN* mutation/deletion.<sup>23</sup> This scheme was validated in a set of pediatric patients; however, it was not upheld when other cooperative groups tested it in their populations.<sup>24</sup> GRAALL more recently used a hybrid capture-based next-generation sequencing (NGS) approach in adults, and validated this approach in pediatric patients, defining low-risk disease as having *NOTCH1* and/or *FBXW7* mutations, *PHF6* mutations, or *EP300* mutations without *N/K-RAS*, *PI3K* pathway (*PTEN*, *PIK3CA*, *PIK3R1*), *TP53*, *DNMT2A*, *IDH1/2*, or *IKZF1* alterations. When combined with WBC count at diagnosis and EOI MRD, this method identified a favorable risk group with a cumulative relapse incidence of 12% at five years, compared to an adverse risk group with 51% cumulative relapse incidence at five years.<sup>25</sup> This NGS-based stratification needs to be validated by other groups.

A recent landmark study by Pölönen and colleagues performed whole genome, exome, and transcriptome sequencing on more than 1,300 T-ALL cases to better understand T-ALL biology and determine predictors of relapse and treatment failure. This study identified genetic drivers in 95% of cases, defining 15 subtypes of T-ALL, some of which were novel. One of the new proposed subtypes was termed 'ETP-like'. This is enriched in, but not limited to, the ETP and near ETP immunophenotypes and defined by a distinct gene expres-

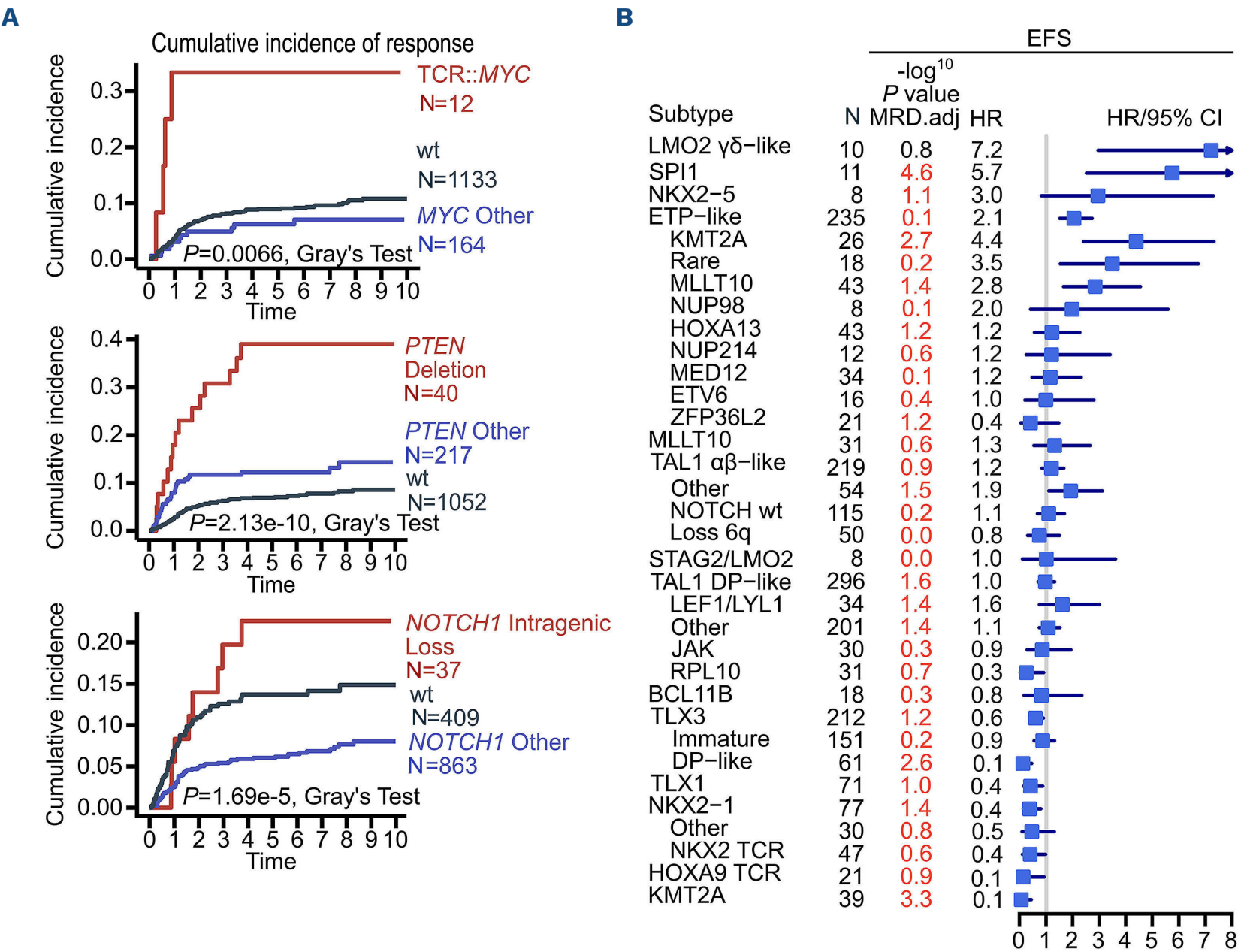


sion profile.<sup>6</sup> Patients with ETP-like disease were found to have inferior outcomes regardless of immunophenotype. In contrast, patients with the ETP immunophenotype only had inferior outcomes if they were in the ETP-like genomic subtype. Pölönen and colleagues demonstrated that in approximately 60% of cases the primary leukemic driver involved non-coding regions of the genome, underscoring the need for whole genome sequencing for characterization of T-ALL. Interestingly, specific types of genetic alterations, rather than solely the gene, were found to have specific outcome associations. For example, intragenic loss and intronic single nucleotide variants (SNV) in *NOTCH1* were associated with poor outcome whereas other types of *NOTCH1* alterations were associated with favorable outcomes. *LMO2* intergenic loss, *NOTCH1* intragenic deletions, *TCR::MYC*, and *PTEN* deletions, among others, were specifically associated with relapse (Figure 1A). Within the ETP-like subtype, cases were divided into further genetic subgroups based on specific driver mutations, for example ETP-like KMT2A and ETP-like MLLT10 groups, each with prognostic value. Individually, the poorest survival outcomes were seen with SPI1 and LMO2  $\gamma\delta$ -like subtypes, and

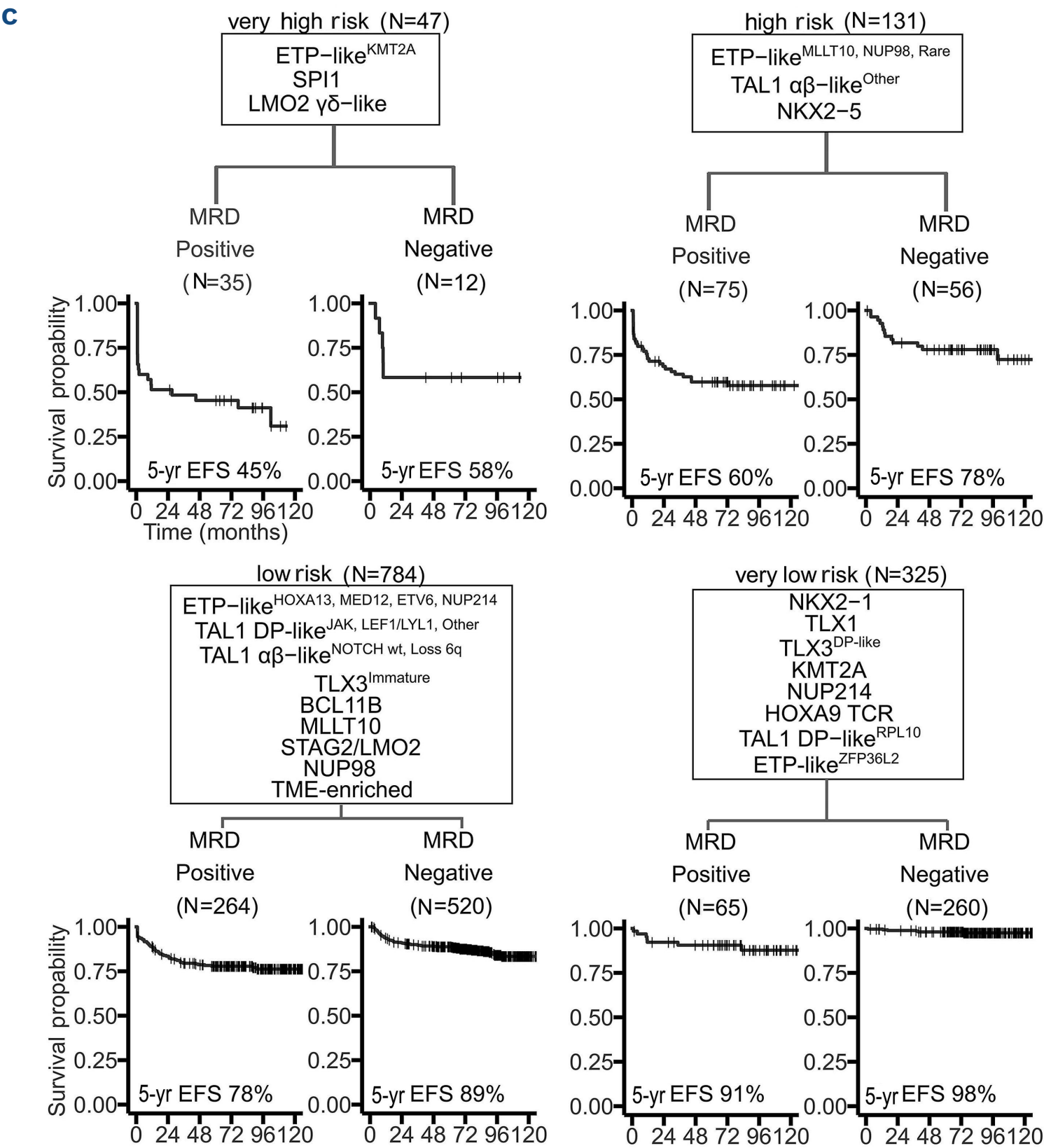
ETP-like KMT2A, and ETP-like MLLT10 subgroups (Figure 1B). Subtype superseded specific driver mutation. For example, unlike genetic subgroups within the ETP-like group, the non-ETP-like KMT2A and the non-ETP-like MLLT-10 subgroups had favorable prognosis. Two separate multivariate models were constructed that incorporated subtype, gene alterations, and pathway dysregulation information to stratify patients into risk groups. The highest risk for relapse was seen with features including ETP-like KMT2A, SPI1, and LMO2  $\gamma\delta$ -like subtypes (5-year EFS <60%) whereas ETP-like ZFP36L2, TAL1 DP-like RPL10, TLX1, KMT2A (non-ETP-like), and HOXA9 TCR, among others, had favorable outcomes (5-year EFS >98%) (Figure 1C).<sup>6</sup>

Established therapies for relapsed disease

Re-induction therapy at relapse typically consists of multi-agent chemotherapy to achieve complete response (CR), in addition to chemotherapy administered directly to the CNS to eliminate CNS disease or prevent spread. The goal



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**Figure 1. Whole genome, exome, and transcriptome sequencing of more than 1,300 cases of T-cell acute lymphoblastic leukemia has redefined the genetic landscape of T-cell acute lymphoblastic leukemia and created a new understanding of risk for relapse.** (A) Cumulative incidence of relapse varies significantly depending on specific type of genomic alteration in the same gene (time in months). (B) Forest plot of T-cell acute lymphoblastic leukemia (T-ALL) comparing clinical outcome by event-free survival (EFS) for each of 15 subtypes compared to the whole, with significant associations ( $P<0.1$ ) in red. (C) 15 T-ALL subtypes categorized into 4 risk groups, and subdivided by end of induction measurable residual disease (EOI MRD) (negative = MRD<0.1%) to stratify patients into outcome groups ranging from 5-year EFS 45–98%. adj.: adjusted; CI: Confidence Interval; HR: Hazard Ratio; OR: Odds Ratio; wt: wild-type. Adapted from Pölönen et al.<sup>6</sup>

of treatment at relapse is to achieve a second remission, ideally without detectable MRD, to bridge to HSCT which is the only proven curative treatment for relapsed T-ALL and T-LBL, regardless of relapse site or timing.<sup>26</sup> Outcomes of HSCT for relapsed T-ALL are improved when total body irradiation (TBI) is included in conditioning,<sup>27</sup> and are superior for patients with isolated extramedullary relapse.<sup>28</sup>

There are multiple reinduction regimens that have been used in r/r T-ALL/T-LBL. Most commonly these include a 4-drug re-induction (vincristine, corticosteroid, asparaginase, anthracycline) with or without a newer agent. Four multi-agent regimens often used in pediatrics are shown in Table 2. As response rates are similar overall for each of the reinduction regimens based on early phase trials, the

choice is often based on access to agents, prior toxicities or reactions to medications, CNS status at relapse, timing of relapse, and recent chemotherapy exposure. Importantly, each of these re-induction regimens were tested in relatively small, non-randomized, early phase trials in different eras with different standard therapy for newly diagnosed patients, making comparison between regimens challenging.

UKALLR3 is an intensive dexamethasone-based regimen containing mitoxantrone, established as an effective approach for r/r pediatric ALL with studies reporting 85% complete response (CR), 62% MRD-negative rate, 3-year progression-free survival (PFS) and OS of 65% and 69%; however, approximately 90% of patients had B-ALL.<sup>29,30</sup> A more recent study evaluated the use of UKALLR3 in a larger number of pediatric patients with r/r T-ALL and reported 29% and 33% 10-year EFS and OS.<sup>31</sup> Multiple studies have shown the UKALLR3 regimen has significant toxicity with high-rates of treatment-related mortality. Thus, despite the high response rates (at least for B-ALL<sup>32,33</sup>), it is less commonly used.<sup>34</sup> ALL-REZ BFM 2002 is an alternate regimen of intensive multi-agent chemotherapy that includes dexamethasone but varied significantly from UKALLR3 in dose, schedule, and type of chemotherapeutics. ALL-REZ BFM 2002 was compared to UKALLR3 in relapsed ALL in a

randomized international multi-center trial<sup>33</sup> and achieved similar outcomes to UKALLR3 with 27% and 30% 10-year EFS and OS, respectively, for patients with r/r T-ALL.<sup>31</sup> Combining outcomes for patients with r/r T-ALL treated on the UKALLR3 and AALL-REZ BFM 2002 trials, 64% of 115 patients had CR after the first block of treatment.<sup>31</sup> Data comparing outcomes between UKALLR3 and ALL-REZ BFM 2002 limited to patients with T-ALL are still to be published. An alternate regimen, using a less-intensive prednisone-based 4-drug regimen plus the proteasome inhibitor bortezomib, was studied on the COG AALL07P1 trial. This included 32 patients with pediatric T-ALL/LBL, achieving CR 68% (15/22), and MRD <0.01% in 20% of T-ALL cases at end of block 1. Sub-analysis of 20 evaluable patients with T-ALL stratified by MRD status at the end of block 1 demonstrated 3-year survival rates of 75% EFS and 67% OS for patients who were MRD-negative (N=4), and 43% EFS and 44% OS for those MRD-positive (N=16).<sup>35</sup> The DELPHINUS trial (*clinicaltrials.gov Identifier: NCT03384654*) investigated the combination of the anti-CD38 monoclonal antibody daratumumab with a multi-agent chemotherapy backbone. This backbone was similar to AALL07P1 except for fewer doses of pegaspargase, and it did not include bortezomib. Response rates for 29 children and young adults with r/r T-ALL were promising with

**Table 2.** Established multi-agent regimens for relapsed/refractory T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma.

Regimen	Re-induction (block 1)	Outcomes in r/r T-ALL/LBL	Comments	Ref
UKALL R3 (mitoxantrone arm <sup>29</sup> )	Vincristine, dexamethasone, asparaginase, mitoxantrone	10-year EFS 29%, 10-year OS 33% (N=21)	Associated with high rates of infections, e.g., 40% of pts on AALL1331 had grade ≥3 infection due to UKALL R3 reinduction, <sup>34</sup> other studies reporting rates as high as 90%. <sup>30</sup>	31
ALL-REZ BFM 2002	Dexamethasone, vincristine, methotrexate, asparaginase, cytarabine	10-year EFS 27%, 10-year OS 30% (N=67)	Increased cumulative dosing of chemotherapy compared to UKALL R3.	31
AALL07P1	Bortezomib plus VPLD	T-ALL (N=22): CR 68%, MRD-neg rate 20%, 3-year EFS/OS 75%/67% when MRD-neg after block 1 (N=4), 3-year EFS/OS 43%/44% when MRD-pos after block 1 (N=16). T-LBL (N=10): CR 30%, ORR 70%	Bortezomib overall well-tolerated with most common toxicity being hematologic (55%). Grade 3 neuropathy in 3%, no grade >3 neuropathy. Overall infection grade ≥3 rate 21-29% (N=146).	35
DELPHINUS	Dara plus VPLD	T-ALL (N=29): CR+CRi 83% after block 2, MRD-neg rate 41%, HSCT rate 72%, 2-yr EFS/OS 33%/39%. T-LBL (N=10): CR 40%, ORR (CR+PR) 50% after block 2, MRD-neg rate 50%, HSCT rate 30%, 2-yr EFS/OS 20%	Grade ≥3 infection in 44% of pts with T-ALL/LBL. No TEAE related to Dara. Dara IRR occurred in 72% of pts with T-ALL/LBL, primarily abdominal pain, vomiting, pyrexia, cough. 2 of 28 IRR were greater than grade 2. Dara exposure was associated with decreased CD38 expression on blasts.	36
NECTAR	Nelarabine, cyclophosphamide, etoposide	T-ALL (N=12): CR 25%, ORR 33%, HSCT rate 42%; T-LBL (N=9): CR 33%, ORR 44%, HSCT rate 56%	Grade ≥3 neurotoxicity in 13% (N=23).	38

CR: complete response; CRi: complete response with incomplete count recovery; Dara: daratumumab; EFS: event-free survival; HSCT: hematopoietic stem cell transplantation; IRR: infusion-related reaction; MRD: minimal residual disease; MRD-neg: MRD-negative; MRD-pos: MRD-positive; N: number; ORR: overall response rate; OS: overall survival; PR: partial response; pts: patients; r/r T-ALL/LBL: relapsed/refractory T-cell acute lymphoblastic leukemia / lymphoblastic lymphoma; Ref: reference; TEAE: treatment-ending adverse event; VPLD: vincristine, prednisone, asparaginase, doxorubicin; yr: year.



an overall response rate (ORR) of 83% (CR plus CR with incomplete hematologic recovery [CRi]) after 2 blocks of therapy and a 41% MRD-negativity rate. 72% of patients were successfully bridged to HSCT. Overall survival was reported as 33% EFS and 39% OS for patients with T-ALL<sup>36</sup> (Table 2). The purine nucleoside antimetabolite nelarabine was initially studied as monotherapy for r/r disease and demonstrated CR 48% and ORR 55% (N=33) in children with first relapse of T-ALL.<sup>37</sup> Nelarabine can cause neurotoxicity that can be permanent. The NECTAR regimen combining nelarabine with cyclophosphamide and etoposide was recently published, reporting 25% CR and 33% ORR (N=12) with 42% of patients going to HSCT for T-ALL<sup>38</sup> (Table 2). Of note, these trials were in different eras and therapy for newly diagnosed patients has intensified, potentially explaining the inferior results of NECTAR as compared with nelarabine monotherapy. Access to nelarabine is limited outside of North America.

## Precision therapies

Inhibition of molecular pathways responsible for oncogenesis has proven effective for some forms of ALL. The prototypical example is the use of tyrosine kinase inhibitors, such as imatinib, dasatinib, and ponatinib, for *BCR::ABL1* (Philadelphia chromosome positive [Ph<sup>+</sup>]) ALL which, when combined with cytotoxic chemotherapy, has significantly improved overall outcomes compared to chemotherapy alone.<sup>39,40</sup> Several approaches with preclinical or clinical experience in T-ALL/LBL are summarized in Table 3, with notable agents detailed below.

### BCL-2 and BCL-X<sub>L</sub>

The B-cell lymphoma-2 (BCL-2) family of proteins regulate apoptosis through both pro- and anti-apoptotic activity. Several subtypes of ALL have been found to be dependent on anti-apoptotic BCL-2 family proteins, particularly BCL-2, BCL-X<sub>L</sub>, and MCL-1, for survival and, therefore, sensitive to blockade by BH3-mimetic drugs. Profiling of T-ALL cell lines and primary samples found that ETP-ALL has specific dependence on BCL-2, while non-ETP-ALL was more dependent on BCL-X<sub>L</sub>.<sup>41</sup>

Venetoclax, a BCL-2 inhibitor, has shown efficacy in r/r ETP-ALL when combined with various combinations of chemotherapy.<sup>42</sup> Navitoclax, a dual BCL-2/BCL-X<sub>L</sub> inhibitor, was recently studied in combination with venetoclax and multi-agent chemotherapy in adults and children with r/r ALL in a phase I clinical trial and reported combined outcomes for pediatric patients (B- and T-ALL, N=12) receiving a range of cycles of therapy with 75% CR, 50% MRD-negative rate, and 12-month OS of 61%. For all patients with T-ALL (all ages, N=19) receiving a range of therapy cycles, CR was 53%, 32% were MRD-negative, and 12-month OS was 30%.<sup>43</sup> These results led to additional trials combin-

ing venetoclax with navitoclax for r/r T-ALL/LBL; however, these trials were stopped because navitoclax is no longer available even in an investigational setting. Inhibition of BCL-2 +/- BCL-X<sub>L</sub> is an area of intense interest, and several other inhibitors are in development with the potential for utility in r/r T-ALL/LBL (Table 3).

### Cyclin-dependent kinases 4/6

Cyclin-dependent kinases are involved in cell cycle progression, transcription, and DNA repair, and are attractive therapeutic targets in hematologic malignancies where they are frequently over-expressed.<sup>44</sup> In T-ALL, >70% of cases have genetic alterations leading to CDKN2A/B loss, which often leads to concomitant upregulation of CDK4/6.<sup>14</sup> CDK4 and CDK6 complex with D-type cyclins, which function to phosphorylate Rb releasing it from repressive Rb-E2F complexes and promoting G1-S cell cycle progression.<sup>45</sup> CDK6 has been found to be required for both Notch1- and AKT-driven disease.<sup>46,47</sup>

The CDK4/6 inhibitors palbociclib and ribociclib have shown promising results in preclinical models of T-ALL.<sup>45,46</sup> Ribociclib synergized with glucocorticoids and mTOR inhibitors in mice, which prompted the launch of a phase I clinical trial treating pediatric patients with ribociclib, everolimus, and dexamethasone (*clinicaltrials.gov Identifier: NCT03740334*).<sup>48</sup> A separate phase I pediatric ALL trial, COG AINV18P1 (*clinicaltrials.gov Identifier: NCT03792256*), treated children with r/r T- and B-ALL with palbociclib added to a prednisone-based 4-drug reinduction; palbociclib was well-tolerated and 2 of 4 patients with multiple-relapsed T-ALL achieved CR.<sup>49</sup>

### Jak/Stat

Aberrant Jak/Stat signaling is common in T-ALL, particularly in ETP and ETP-like ALL, often through activating mutations in *JAK1*, *JAK3*, *STAT5*, and *IL7Rα*, *JAK2* fusions, or *PTPN2* deletions.<sup>12,50</sup> The Jak1/2 inhibitor ruxolitinib was found to be effective independent of Jak/Stat pathway mutations in preclinical ETP models.<sup>51</sup> *IL7R* mutations are associated with glucocorticoid resistance, and ruxolitinib has been shown to reverse glucocorticoid resistance and synergize with glucocorticoid treatment in preclinical models.<sup>52</sup>

Case reports have demonstrated clinical response to Jak inhibitors in r/r T-ALL/LBL harboring *JAK3* mutations.<sup>53</sup> Additionally, BH3 profiling and transcriptome sequencing of over 100 pediatric T-ALL cases identified *JAK3* activating mutations as being strongly associated with mitochondrial apoptosis resistance.<sup>54</sup> Prospective trials are needed to ascertain the efficacy of Jak inhibition, either as monotherapy or as part of a multi-agent regimen.

### Lymphocyte-specific protein tyrosine kinase

Lymphocyte-specific protein tyrosine kinase (LCK) is an SRC-family tyrosine kinase and member of the pre-TCR pathway required for normal T-cell development.<sup>55</sup> Dasat-

**Table 3.** Precision therapies for relapsed/refractory T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma.

Target	Therapeutic agent	Details on therapy or therapeutic agent	Clinical and preclinical outcomes	Ref
BCL-2 / BCL-X <sub>L</sub>	Venetoclax + navitoclax	Combination with VAD	Pediatric r/r ALL (~50% T-cell disease): CR 75%, ORR 83%, MRD-neg 50%, 12-mo-OS 61% (N=12). T-ALL/LBL all ages: CR/ORR 57%, MRD-neg 33%, 12-mo-OS 30%(ALL) 67%(LBL) (N=21). Common study drug-related TEAE were neutropenia and thrombocytopenia.	43
	Venetoclax + navitoclax	Combination with VAD at investigator's discretion	Pediatric r/r ALL/LBL (~50% T-cell disease): CR 71%, ORR 86% (N=7). T-ALL/LBL all ages: CR/ORR 44%, MRD-neg 31%, 22% went to HSCT. Common study drug-related TEAE were hematologic.	84
	Venetoclax	Combination with multimodal cytotoxic chemo	Retrospective analysis of pediatric r/rT-ALL/LBL at single institution: CR 75%, median PFS 4-mo, OS 7.7-mo (N=8). Common study drug-related TEAE were neutropenia, thrombocytopenia, elevated bilirubin, and sepsis.	85
	LP-118	Next-gen dual BCL-2/BCL-XL inhibitor	Preclinical - effective against primary CLL cells resistant to venetoclax. Currently in phase I trial for hematologic malignancies ( <i>clinicaltrials.gov Identifier: NCT04771572</i> ).	86
	Lisaftoclax (APG-2575)	Next-gen BCL-2 inhibitor	Preclinical - overcomes resistance to venetoclax. Recently studied in phase I/II trial for hematologic malignancies (not including T-ALL) ( <i>clinicaltrials.gov Identifier: NCT04494503</i> ).	87
	Palcitoclax (APG-1252)	Next-gen dual BCL-2/BCL-XL inhibitor	Preclinical - avoids hematologic toxicity (thrombocytopenia) seen with navitoclax, effective in model of peripheral T-cell lymphoma.	87
	Sonrotoclax (BGB-11417)	Next-gen BCL-2 inhibitor	Preclinical - increased potency overcomes resistance to venetoclax, effective in models of venetoclax-resistant hematologic malignancies.	88
	DT2216	BCL-X <sub>L</sub> PROTAC	Preclinical - increased potency in cancer cells plus less-toxic to platelets, effective in xenograft models. Recently studied in phase I trial for r/r malignancies ( <i>clinicaltrials.gov Identifier: NCT04886622</i> ).	89
CDK4/6	S65487	Next-gen BCL-2 inhibitor	Preclinical - effective in models of venetoclax-resistant hematologic malignancy. Currently under investigation for hematologic malignancies ( <i>clinicaltrials.gov Identifier: NCT03755154</i> , <i>clinicaltrials.gov Identifier: NCT04742101</i> ).	90
	AZD0466	Dual BCL-2/BCL-X <sub>L</sub> inhibitor with improved biodistribution	Preclinical - activity against venetoclax-resistant disease. Recently in phase I/II trial for hematologic malignancies ( <i>clinicaltrials.gov Identifier: NCT04865419</i> ).	87
	Palbociclib	+ 4-drug reinduction	Pediatric T-ALL/LBL: CR 50% (N=4).	49
Jak/Stat	Ribociclib	+ everolimus / dexamethasone	Preclinical: T-ALL cell lines and orthotopic mouse models are sensitive to ribociclib, and there is synergy in combination with corticosteroids and/or mTOR inhibition. In phase I trial for r/r ALL ( <i>clinicaltrials.gov Identifier: NCT03740334</i> ).	48
	Ruxolitinib	-	Effective in PDX models of ETP-ALL. Induced CR in a patient with extramedullary relapse of T-ALL ( <i>JAK3</i> -mutated) for 5 mo. Effective for glucocorticoid-resistant T-ALL in preclinical models.	51,53
LCK	Tofacitinib + ruxolitinib	Broader Jak inhibition	Induced remission for 10 mo in a patient with relapsed T-PLL ( <i>JAK3</i> -mutated).	91
	Dasatinib	-	Extensive preclinical data demonstrating efficacy for T-ALL. Single case reports of time-limited efficacy as monotherapy on the basis of <i>ex vivo</i> drug profiling, on basis of <i>ABL1</i> fusion, or <i>ABL1</i> amplification, or <i>PDGFRβ</i> fusion coupled with <i>ex vivo</i> drug profiling.	56, 58, 59, 92
Gamma secretase	PROTAC-mediated LCK inhibition	-	Preclinical - improved efficacy in mouse models.	60
	CD-103 (limantrafin)	Pan-transcriptional Notch inhibitor	Outcomes for T-cell disease not reported.	61
	LY3039478 (crenigacestat)	Pan-transcriptional Notch inhibitor	Limited efficacy for adults with r/r T-ALL/LBL.	
	MK-0752	Pan-transcriptional Notch inhibitor	Limited efficacy for adults/peds with r/r T-ALL.	
	PF-03084014 (nirogacestat)	Reversible Notch inhibitor	8 adults with T-ALL treated, 1 had CR that lasted for 3 mo.	
	MRK-560	PSEN-1 selective	Preclinical - effective and lower toxicity in preclinical models, exhibits synergy with dexamethasone and XPO1 inhibitor.	

Continued on following page.



SERCA	Thapsigargin	Prevents trafficking of gamma secretase to cell surface	Expected to have significant cardiotoxicity, but can be conjugated to folate for T-ALL targeting.	62
	CAD204520	Preferentially targets mutated Notch1 protein	Less cardiotoxicity in murine model.	
PDGFR	Avapritinib	Monotherapy	Given to a child with <i>PDGFRA</i> fusion and separate activating mutation p.D842N, causing >50% reduction in marrow burden and tumor lysis syndrome, although CR was not reached.	63
	CP-673451	-	Preclinical - effective in PDX of T-LBL harboring <i>MYH9::PDGFRB</i> fusion.	93
Extropin 1	KPT-330 (selinexor)	First-generation XPO1 inhibitor	Efficacy in preclinical leukemia models.	64
	KPT-8602 (eltanexor)	Second-generation XPO1 inhibitor	Efficacy in preclinical T-ALL model.	

ALL: acute lymphoblastic leukemia; chemo: chemotherapy; CLL: chronic lymphocytic leukemia; CR: complete response; ETP: early T-cell progenitor; HSCT: hematopoietic stem cell transplant; mo: month; MRD: minimal residual disease; MRD-neg: MRD-negative; N: number; next-gen: next-generation; ORR: overall response rate; PDX: patient-derived xenograft; peds: pediatric patients; PFS: progression-free survival; PROTAC: proteolysis-targeting chimera; r/r T-ALL/LBL: relapsed/refractory T-cell acute lymphoblastic leukemia / lymphoblastic lymphoma; Ref: reference; TEAE: treatment-ending adverse event; T-PLL: T-cell prolymphocytic leukemia; VAD: vincristine, asparaginase, dexamethasone.

inib, an ABL- and SRC-family kinase inhibitor, has been shown to be effective for T-ALL driven by *ABL1* fusion in case reports.<sup>56</sup> More recently, studies have been conducted on *ex vivo* drug profiling. These found 30-44% of T-ALL cases tested were exquisitely sensitive to dasatinib through high expression of LCK.<sup>57,58</sup> Recent work suggests that LCK activation is more common in more mature-lineage T-ALL.<sup>6</sup> Clinical trials and preclinical studies using alternate LCK inhibitors are underway.<sup>59,60</sup>

Notch

The Notch signaling pathway plays a critical role in T-cell differentiation and proliferation and activating Notch pathway mutations are among the most frequent abnormality in T-ALL.<sup>6,14</sup> Notch signaling is dependent on  $\gamma$ -secretase which cleaves the intracellular domain of the Notch receptor, allowing translocation to the nucleus where it activates transcription of several key genes. Several  $\gamma$ -secretase inhibitors (GSI) have been investigated in T-ALL, mostly with limited clinical success (Table 3) and dose-limiting toxicities.<sup>61</sup> Alternate Notch-targeting approaches have been developed and tested in preclinical models, including selective inhibition of PSEN-1 and sarco/endoplasmic reticulum calcium ATPase (SERCA) channel inhibition.<sup>62</sup>

Other small molecule inhibitors

Other promising small molecule inhibitors include PDGFRA inhibitors, such as avapritinib,<sup>63</sup> exportin-1 inhibitors,<sup>64</sup> and OBI-3424 which inhibits AKR1C3. AKR1C3 is highly expressed in several cancers, including T-ALL.<sup>65</sup> Currently, OBI-3424 is being investigated in the S1905 phase II trial (*clinicaltrials.gov Identifier: NCT04315324*).

Immunotherapy for relapsed T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma

Immunotherapy has revolutionized the treatment of several types of cancers, including B-cell malignancies. Unfortunately, translation of immunotherapies for T-ALL/LBL have lagged behind those of B-ALL, based on multiple concerns, including toxicity through elimination of healthy T cells and fratricide. Nevertheless, multiple trials using immunotherapy for T-ALL are ongoing and early results are promising.

Antibody-based therapies

Antibody-based therapies target membrane-bound or extracellular molecules and can be modified to traffic a bound cytotoxic agent specifically to target cells (antibody-drug conjugate [ADC]), or to link endogenous cytotoxic cells to target cells as in the case of bi-specific T-cell engaging antibodies. Antibody-based approaches have been reviewed in detail<sup>66-68</sup> and will be summarized here (Table 4).

**CD38** - Daratumumab is a monoclonal antibody against CD38, a type II transmembrane glycoprotein present on thymocytes, activated T cells, and differentiated B cells. CD38 is highly expressed on most cases of T-ALL and its expression persists at relapse.<sup>67</sup> Preclinical studies using daratumumab in T-ALL have shown promising activity as monotherapy or in combination with chemotherapy, leading to clinical trials such as the aforementioned DELPHINUS trial (Table 2). Despite expression on activated T cells, daratumumab has not been shown to cause T-cell aplasia. The most common side effect is infusion reaction;<sup>36</sup> CD38 is present on mast cells and risk of infusion reactions is high with the first dose

**Table 4.** Antibody-based therapies.

Target	Agent	Therapy details	Clinical outcomes	Ref
CD38	Daratumumab	DELPHINUS (Dara + VPLD)	r/r pediatric T-ALL (N=29): CR+CRi 83% after block 2, MRD-neg rate 41%, HSCT rate 72%, 2-yr EFS/OS 33%/39%. r/r pediatric T-LBL (N=10): CR 40%, ORR (CR+PR) 50% after block 2, MRD-neg rate 50%, HSCT rate 30%, 2-yr EFS/OS 20%.	36
		Dara + ven + CAGE	r/r adult T-ALL/LBL: CR 48%, ORR 57%, 95% went to HSCT, median PFS and OS not reached (median f/u 7.4 mo) (N=21). ETP-ALL: CR 71% (N=7).	94
	XmAb18968	Dara + ven + bortezomib	r/r T-ALL (age 20-30): 100% CR (N=3).	68
		Bispecific T-cell engaging antibody	r/r adult ETP-ALL: 67% CR after 1 cycle (N=3).	67
		Bispecific T-cell engaging antibody	Preclinical - superior efficacy against multiple myeloma cells compared to Dara, preclinical data in T-ALL needed.	71
	CD38-077	Antibody-drug conjugate	Preclinical - effective in models of Burkitt lymphoma and multiple myeloma, preclinical data in T-ALL needed.	68
CD52	Alemtuzumab	Single agent	1/13 pts with r/r ALL had CR, trial closed due to toxicity.	66
		Alemtuzumab added to post-remission therapy	r/r adult T-ALL (N=5), overall effect was to reduce MRD but was associated with viral infections.	
CD25	Basiliximab	Monotherapy	Induced remission in a child with T-ALL and severe dermatologic paraneoplastic syndrome.	66
IL-17RA	Lusvertikimab (OSE-127)	Combination with chemo	Preclinical - MRD negativity in >50% of mouse PDX models.	68
	A7R-ADC-SN-38	Antibody-drug conjugate	Preclinical - effective against IL7RA-expressing B-ALL cell line in mouse model.	22
CD3	Teplizumab	-	Preclinical - effective in preclinical model when paired with etanercept or birinapant.	95
CD47	Hu5F9-IgG2o	Combination with Dara	Preclinical - improved survival in mouse PDX models with modest or no response to Dara alone.	67
Notch1	MAb604.107	Higher affinity for T-ALL-related Notch1 mutation than WT	Preclinical - reduced T-ALL cell proliferation and CD34/CD44-high cells specifically.	96
CD99	10A1 HCscFv	Quadrivalent antibody	Preclinical - induced apoptosis of T-ALL blasts but not healthy PBMC <i>in vitro</i> .	97

B-ALL: B-cell acute lymphoblastic leukemia;; CAGE: cytarabine, alcarubicin, granulocyte colony-stimulating factor, etoposide; CR: complete response; CRi: complete response with incomplete count recovery; Dara: daratumumab; EFS: event-free survival; ETP: early T-cell progenitor; f/u: follow-up; HSCT: hematopoietic stem cell transplant; MRD: minimal residual disease; N: number; OS: overall survival; ORR: overall response rate; PBMC: peripheral blood mononuclear cells; PDX: patient-derived xenograft; PFS: progression-free survival; PR: partial response; r/r T-ALL/LBL: relapsed/refractory T-cell acute lymphoblastic leukemia / lymphoblastic lymphoma; Ref: reference; ven; venetoclax; VPLD: vincristine, prednisone, asparaginase, doxorubicin; WT: wild-type.

but markedly lower with subsequent doses as mast cells do not regenerate quickly. CD38 is expressed at low levels by red blood cells (RBC) and daratumumab can persist on RBC for several months, which can complicate RBC cross-matching but has not been found to cause hemolysis. Special techniques have recently been used to safely transfuse patients with daratumumab.<sup>69</sup> Daratumumab is also being investigated as monotherapy to prevent relapse after HSCT for r/r T-ALL/LBL in an ongoing clinical trial (*clinicaltrials.gov Identifier: NCT04972942*).

A separate CD38-targeting antibody, isatuximab, has been developed which binds a different epitope on CD38 from daratumumab. Two clinical trials investigating isatuximab for hematologic malignancies including T-ALL (*clinicaltrials.gov Identifier: NCT02999633* and *clinicaltrials.gov Identifier: NCT03860844*) were terminated early.

Bispecific antibodies link endogenous cytotoxic T cells to

target cells with a single molecule, inducing destruction of the target cell. Blinatumomab, a CD19/CD3-bispecific is highly effective in relapsed B-ALL.<sup>70</sup> The bispecific CD38-/CD3-binding antibody XmAb18968 showed promise in a small study of 4 adult patients with r/r T-ALL<sup>67</sup> and has been expanded into a larger trial (*clinicaltrials.gov 05038644*). Additional CD38/CD3 bispecific antibodies are being investigated, including ISB1342.<sup>71</sup>

**CD52** - CD52 is expressed on T cells across stages of differentiation, as well as other lymphocytes including B and natural killer (NK) cells. The anti-CD52 antibody alemtuzumab was studied as monotherapy in an early phase trial in children with r/r T-ALL (ADV0222) but stopped early for excessive toxicity.<sup>66</sup>

**CD25** - CD25, the alpha subunit of the receptor for IL-2

(IL2RA), is highly expressed on T-cell malignancies including T-ALL. Published clinical experience with basiliximab, a monoclonal antibody against CD25, is limited to the case of a child with refractory T-ALL complicated by a paraneoplastic rash in whom remission was induced with the administration of basiliximab.<sup>67</sup>

*Additional antibody targets* - CD47 is highly expressed in approximately 50% of T-ALL/LBL and CD47 functions as an immune checkpoint, acting as a ligand for signal regulatory protein alpha (SIRPα) to prevent phagocytosis.<sup>72</sup> Encouraging results combining CD47 blockade with daratumumab were seen in T-ALL preclinical patient-derived xenograft (PDX) models.<sup>67</sup> Several additional targets have been investigated that show promise in preclinical models. The alpha subunit of the IL-7 receptor (IL7RA), also termed CD127, is expressed on 60-80% of T-cell subtypes and has been shown to increase with exposure to multiagent chemotherapy. Anti-IL7R antibodies have shown activity in preclinical models.<sup>67</sup> Notch1, CD3, and CD99 are also being explored as targets for antibody therapy for T-ALL (Table 4).

Cellular therapies

Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of B-cell malignancies including B-ALL, achieving impressive outcomes especially in the r/r setting, with some studies showing remission rates >90% and very high rates of MRD negativity among highly refractory patients.<sup>73</sup> CAR T-cell therapy for T-cell disease has a number of challenges (reviewed by Dourthe et al.<sup>74</sup>). These include fratricide, which can occur when the target antigen is present on both malignant cells and CAR-T cells. Techniques to prevent fratricide focused on masking or deletion of the target antigen from CAR-T have shown promise. Product contamination with malignant cells is a theoretical concern; however, T-ALL blasts do not survive ex vivo and have not been seen in products after development. Targeting antigens present on healthy T cells risks T-cell aplasia with risk of severe infections. The aggressive nature of T-ALL/LBL embodies challenges to CAR-T in that the disease is often rapidly progressive, limiting the time available for CAR-T manufacturing, and the intense regimens used to treat T-ALL/LBL limit the number of healthy endogenous T cells available for manufacturing. To avoid these issues,

Table 5. Chimeric antigen receptor-T products.

Target	Cell source	Pre-infusion manupulation / fratricide avoidance	Outcomes	Toxicities	Ref
CD7	Auto	In vitro “natural selection” via fratricide	60 pts (19 ≤14 yr): 94.4% CR at 1 mo, 2-yr OS 63.5%, 2-yr PFS 53.7%. Separate study: 10 pts ≤14 yr with r/r T-ALL/LBL treated with CAR-T followed by HSCT had LFS and OS 87.5% at 2 yr.	CRS in 91.7% of pts (11.7% grade ≥3), ICANS in 5% (1.7% grade ≥3), infection in 37% (17% grade ≥3) including 8% viral reactivation.	77,78
	Auto	CD7 kd with PEBL	17 pts (13 pediatric): 94% MRD-neg CR at 1 mo, 2-yr OS 55%, 53% went to HSCT and all in remission at time of report.	CRS in 76% of pts (0% grade ≥3), ICANS in 12% (all grade 1), infection in 47% (29% grade ≥3). No persistent T-cell aplasia (CD7 <sup>+</sup> T-cell expansion).	79
	Auto	CD7 nanobody expression	8 adults: 88% CR (7/8), 100% of pts with BM involvement (6/6) had MRD-neg CR, 4/7 relapsed within 12 mo.	88% (7/8) with any CRS, 1/7 with CRS grade ≥3, no ICANS. No persistent T-cell aplasia (CD7 <sup>+</sup> T-cell expansion).	76
	Auto	CD7 kd with IntraBlock PEBL	5 adults: 2/5 had CR and 1/5 had PR. 3/3 pts with objective response relapsed with CD7 <sup>+</sup> T-ALL.	CRS in 60% (grade ≥3 in 20%), none had ICANS. 2 of 5 developed IEC-HS. 2/5 had viral reactivation.	80
	Allo	CD7 kd with IntraBlock PEBL, derived from matched donors	20 adults: 85% CR, 95% ORR by 1 mo, 35% went to HSCT, 37% PFS and 42% OS at 2 yr.	100% of pts had CRS, 2/20 grade ≥3, 3/20 had ICANS (all grade 1). 30% had infection (25% grade ≥3), 80% had GvHD (5% grade ≥3). 100% had cytopenia, ALC returned to normal in ~50% with CD7 <sup>+</sup> T cells.	
	Allo	CD7 kd with IntraBlock PEBL, derived from matched donors	2 pediatric pts, CAR-T followed by haplo-HSCT (same donor): 100% CR and no relapse at time of report (>2yr).	CRS grade 2 in 100%, 1 had GvHD in skin and liver. 1 pt had HHV6 reactivation prior to HSCT, then EBV and CMV reactivations after HSCT with PTLD and CMV retinitis.	98

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CD7	Allo	CRISPR ko of CD7 and TRAC (GvHD prevention)	12 adults: 58% CR, 50% MRD-neg CR, 17% to HSCT.	CRS in 78% (5% grade $\geq 3$ ), ICANS in 5% (grade 1), no GvHD prolonged T-cell aplasia.	82
	Allo	CRISPR ko of CD7 for fratricide, TRAC, IL7Ra induction (survival)	12 adults: 92% CR at 1 mo, one went to HSCT, 4 pts had relapse within 5-10 mo. 2 pts were still in CR at time of report, 1 at almost 1 yr the other at 3 yr.	83% with any CRS, 67% with CRS grade 3. No ICANS. Endogenous T cells recovered over time but remained low at 6 mo.	99
	Allo	CRISPR ko of CD7, TCR, HLA-II (GvHD prevention); E-cadherin induction to prevent NK-cell attack.	11 adults with T-ALL/LBL and 1 with AML (CD7 <sup>+</sup> ): 64% CR, 82% ORR, 27% went to HSCT. 57% (4/7) pts with initial CR remained in CR at median f/u of 10.5 mo.	CMV and/or EBV reactivation seen in several pts, including 1 pt developed EBV-associated DLBCL after CR and died.	76
	Allo	Base-editing to inactivate CD7, TRBC (GVHD prevention), CD52 (avoid serotherapy)	3 children with relapsed T-ALL: 67% CR followed by HSCT and still in remission at time of report.	3/3 any CRS, 1/3 with grade $\geq 3$ CRS; 1/3 with ICANS (grade 1), 2/3 had CMV reactivations and 1 died of fungal infection.	76
	Auto	<i>Ex vivo</i> selection of naturally-occurring CD7 <sup>+</sup> T cells using magnetic beads	Preclinical - CD7 <sup>+</sup> CAR-T retained potent antitumor activity and outperform CAR-T made from bulk (predominantly CD7 <sup>+</sup> ) T cells.	-	76
	Auto	CD7 CAR construct insertion at CD7 locus, disrupting CD7 expression	Preclinical - effective in mouse xenograft model of T-ALL.	-	76
	Allo	Cytosine base editing to ko expression of CD7, CD52, TRAC, PD1 (avoid CAR-T silencing)	Preclinical - effective in mouse PDX models of T-ALL.	-	81
	Allo	CRISPR ko of CD7 and TRAC	Preclinical - effective in mouse xenograft models of T-ALL.	-	76
CD5	Auto	None	9 pts (8 adults, 1 YA) with r/r T-ALL/NHL: 33% CR, 44% ORR.	33% (3/9) any CRS, none grade $\geq 3$ . 11% (1/9) with ICANS (grade 2). 22% (2/9) with cytopenias $>35$ d. 1 pt had CMV and BK virus reactivation.	66
	Allo	CRISPR ko of CD5, tEGFR "off" switch	3 adults with r/r T-NHL, 33% CR, 100% ORR.	100% CRS (grade 1) followed by severe rash refractory to CS necessitating centuximab for "off" switch.	83
CD3		TALEN-mediated disruption of TCR	Preclinical - effective in mouse PDX model of T-ALL.	-	100
CD4		None	Preclinical - effective against mouse xenograft model of T-NHL.	-	66
CD38		None	Preclinical - effective against mouse PDX models of T-ALL, AML, MM.	-	101
CD1a		None	Preclinical - effective against mouse PDX model of cortical T-ALL.	-	66
CD2	Allo	CRISPR ko of CD2 and TRAC	Preclinical - effective against mouse PDX models of T-ALL and CTCL.	-	102
CCR9		None	Preclinical - effective against mouse PDX models of T-ALL.	-	67
TRBC1/2		None	Preclinical - effective against mouse xenograft model of T-ALL.	-	66

ALC: absolute lymphocyte count; allo: allogeneic; auto: autologous; AML: acute myeloid leukemia; BM: bone marrow; CAR-T: chimeric antigen receptor T cell; CMV: cytomegalovirus; CR: complete response; CRISPR: clustered regularly interspersed short palindromic repeats; CRS: cytokine release syndrome; CS: corticosteroids; CTCL: cutaneous T-cell lymphoma; d: days; DLBCL: diffuse large B-cell lymphoma; EBV: Epstein-Barr virus; GvHD: graft-versus-host disease; haplo: haplo-identical; HHV6: human herpesvirus 6; HSCT: hematopoietic stem cell transplant; ICANS: immune effector cell-associated neurotoxicity syndrome; IEC-HS: immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; kd: knockdown; ko: knockout; LFS: leukemia-free survival; MM: multiple myeloma; mo: month; MRD: minimal residual disease; MRD-neg: MRD-negative; N: number; NHL: non-Hodgkin lymphoma; NK: natural killer; ORR: overall response rate; OS: overall survival; PDX: patient-derived xenograft; PEBL: protein expression blocker; PFS: progression-free survival; PR: partial response; Pt: patient; PTLT: post-transplant lymphoproliferative disorder; r/r T-ALL/LBL: relapsed/refractory T-cell acute lymphoblastic leukemia / lymphoblastic lymphoma; Ref: reference; TALEN: TAL effector nuclease; TCR: T-cell receptor; tEGFR: truncated epidermal growth factor receptor; T-NHL: T-cell NHL; TRAC: T-cell receptor alpha constant; YA: young adult; yr: years.

genetically modified “off-the-shelf” allogeneic CAR T-cell products have been developed and these are currently undergoing clinical trials (Table 5).

Natural killer cells functionalized with CAR (CAR-NK) may be attractive for T-ALL therapy as they may help avoid fratricide (limited expression of T-cell markers), and may be more readily used as allogeneic “off-the-shelf” products.<sup>75</sup>

**Cell therapy targets** - CD7 is expressed highly on the majority of cases of T-ALL. Evaluation of 49 T-ALL cases detected CD7 expression on blasts in 94%; similar expression has been seen after chemotherapy and at relapse.<sup>76</sup> CD7 is also expressed on most healthy T cells and NK cells. Several CAR-T products targeting CD7 have been developed (Table 5). One product which survives fratricide without external manipulation (‘natural selection’) has been used in a relatively large number of patients and achieved CR at one month in >90% of patients and 2-year PFS >50% with a tolerable toxicity profile (N=60 adult and pediatric patients).<sup>77</sup> The same CAR-T product was effective when followed by HSCT for pediatric patients with r/r T-ALL/LBL, with a 2-year leukemia-free survival (LFS) of 87.5% (N=10).<sup>78</sup> A separate CD7-targeted CAR-T has down-regulated CD7 by a protein expression blocker (PEBL) and was studied in a cohort of 17 patients with r/r T-ALL (13 pediatric), achieving 94% MRD-negative CR within one month, with mild toxicities. Over a median follow-up of 15 months, there were 2 cases of relapse (one CD7<sup>-</sup>), 24-month OS was estimated at 55% with cumulative incidence of relapse and remission failure of 27%.<sup>79</sup> T-cell depletion is a common finding with CD7 CAR-T, but fortunately T-cell aplasia is not seen. Rather, polyclonal CD7<sup>-</sup> T cells have been found to expand while CD7 CAR-T persist and have at least some anti-infectious activity.<sup>79</sup>

Allogeneic products have been developed which utilize T cells for CAR-T from healthy donors, including one that derives CAR-T from HLA-matched donors and incorporates protein expression blocker (PEBL) to avoid fratricide. Impressive results were seen in the 20 pediatric and adult patients with relapsed T-ALL who received this CAR-T, with 85% CR and 95% ORR by day 30. At a median follow-up of 27 months, 6 patients had relapse with 4 being CD7<sup>-</sup>; 2-year PFS was 37% and 2-year OS 42%. All patients had mild cytokine release syndrome (CRS) and cytopenias with eventual expansion of CD7<sup>-</sup> T and NK cells, and 80% developed any grade graft-versus-host disease (GvHD) (5% grade ≥3). It is notable that 6 of the 12 patients who did not have consolidating HSCT after CAR-T had infection, 5 of whom had severe (grade ≥3) infection, while one patient of the 7 who did have HSCT had severe infection,<sup>80</sup> raising concern for the efficacy of CD7<sup>-</sup> immune cells that expand in the setting of CAR-T persistence. HSCT may be needed following CD7 CAR-T even in the absence of universal T-cell aplasia.

Universal donor (“off-the-shelf”) CAR-T products targeting CD7 that do not require HLS-matched donors, making them more clinically available, have also been developed. One product

**Table 6.** Chimeric antigen receptor-natural killer products.

Target	Preclinical efficacy	Ref
CD7	Effective against mouse PDX models of T-ALL	66
CD4	Effective against mouse xenograft model of T-NHL	67
CD5	Effective against mouse xenograft models of T-ALL	67
CD3	Effective against mouse xenograft model of T-ALL	67

PDX: patient-derived xenograft; Ref: reference; T-ALL: T-cell acute lymphoblastic leukemia; T-NHL: T-cell non-Hodgkin lymphoma.

uses cytosine editing to silence expression of CD7, TRAC to prevent GvHD, CD52 to prevent elimination by lymphodepleting serotherapy, and PD-1 to avoid CAR-T silencing, and demonstrated efficacy in murine models of pediatric T-ALL.<sup>81</sup> Another product uses CRISPR/Cas9 to knockout CD7 and TRAC, and, in a pilot study, 58% of adults with r/r T-ALL/LBL reported 58% CR (6 of 7 CR being MRD-negative) and overall mild toxicity with no GvHD or prolonged T-cell aplasia.<sup>82</sup> CD5 is another attractive target as it is expressed on as many as 80% of T-ALL/LBL cases.<sup>76</sup> Clinical studies of CD5-targeted CAR-T are limited. An autologous CD5-targeting CAR-T was tested in patients with r/r T-ALL or T-cell non-Hodgkin lymphoma (T-NHL) and achieved CR in 1 of 4 patients with r/r T-ALL and 2 of 5 with T-NHL.<sup>76</sup> An allogeneic product modified to have a molecular “off” switch for safety caused severe skin toxicity in all 3 patients treated, necessitating induction of “off signaling” in each case.<sup>83</sup> Several other promising surface markers have been identified and targeted by cellular therapy products in preclinical studies, including CD1a, CD2, CD3, CD4, and CD38 (Table 5). CAR-NK products targeting various T-cell markers have shown promise in preclinical models as well (Table 6).

Conclusion

Relapsed/refractory T-ALL and T-LBL pose major therapeutic challenges. Several therapies have been developed for T-ALL/LBL, and while many have improved outcomes or shown promise in the preclinical setting, major clinical breakthroughs have yet to be seen. Fortunately, many of these novel therapies continue to hold promise, and there are a number of clinical trials currently underway (Table 7). Recent insights into T-ALL biology have led to improved risk-stratification and the identification of novel targets for small molecule inhibitors. While in its infancy in T-ALL/LBL, several immunotherapies have demonstrated striking efficacy in early phase trials. Of critical concern is the target used for immunotherapy: on-target off-tumor cell killing can cause highly harmful T-cell aplasia or a GvHD-like toxicity. In the setting of treatment with immunotherapies, including CAR-T, whether subsequent HSCT remains required for cure in r/r T-ALL is unknown. Nevertheless, most current

**Table 7.** Open clinical trials for pediatric T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma.

Trial number	Therapy details
NCT03081910	Phase I. Autologous CD5-targeted CAR-T for T-cell malignancies including r/r T-ALL/LBL (USA)
NCT03117751	Phase II/III. Precision medicine strategies (TKI, Jak inhibitors, bortezomib, nelarabine) for T-ALL/LBL (USA)
NCT03132454	Phase I. Palbociclib with sorafenib, decitabine, or dexamethasone for r/r leukemia (USA)
NCT03236857	Phase I. Venetoclax monotherapy for r/r malignancies, completed (USA)
NCT03384654	Phase II. Dara + standard chemo for pediatric and YA with r/r B- or T-ALL/LBL (USA & Europe)
NCT03690011	Phase I. Autologous CD7-targeted CAR-T (non-edited) for T-cell malignancies including r/r T-ALL/LBL (USA)
NCT03740334	Phase I. Ribociclib with everolimus and dexamethasone for r/r ALL (USA)
NCT03829540	Phase I. Autologous CD4-targeted CAR-T for r/r T-ALL/LBL (USA)
NCT04029688	Phase I/II. Idasanutlin as single agent or with chemo or ven for pediatric and YA with acute leukemias or solid tumors (International)
NCT04599556	Phase I. Autologous CD7-targeted CAR-T for CD7+ hematologic malignancies including r/r T-ALL/LBL (China)
NCT04840875	Phase I. Autologous CD7-targeted CAR-T for VHR T-ALL/LBL (China)
NCT04860817	Phase I. Autologous CD7-targeted CAR-T, CD7 blockade with ER anchor for r/r T-ALL/LBL(China)
NCT04972942	Phase I. Dara after TBI-conditioned allogeneic HSCT for VHR T-ALL/LBL (USA)
NCT04996160	Phase I. Palbociclib with dexamethasone, bortezomib, doxorubicin for r/r ALL (USA)
NCT05043571	Phase I. Autologous CD7-targeted CAR-T, CD7 blockade with PEBL for r/r T-ALL (Singapore)
NCT05291055	Phase I. Autologous CD7-targeted CAR-T for CD7+ hematologic malignancies including r/r T-ALL/LBL (China)
NCT05397184	Phase I. Allogeneic base-edited CD7-targeted CAR-T for r/r T-ALL (UK)
NCT05032599 NCT05487495	Phase I. HSCT donor-derived CD5-targeted CAR-T for r/r T-ALL/LBL (China)
NCT05658640	Phase I/II. Trametinib with dexamethasone cyclophosphamide, and cytarabine for r/r ALL/LBL with RAS/RAF/MAPK alterations. This sub-protocol is part of a larger master protocol HEM-iSMART using detailed molecular characterization to allocate patients to different targeted therapies. (Netherlands)
NCT05885464	Phase I/II. Allogeneic quadruple base-edited CD7-targeted CAR-T (BEAM-201) for r/r T-ALL/LBL(USA)
NCT06064903	Phase I/II. Autologous CD7-targeted CAR-T, CD7 expression blockade with PEBL for r/r T-ALL/LBL(Italy)
NCT06326463	Phase I. Autologous CD70-targeted CAR-T for hematologic malignancies including CD70+ r/r T-ALL/LBL (USA)

CAR-T: chimeric antigen receptor T-cell; chemo: chemotherapy; Dara: daratumumab; ER: endoplasmic reticulum; HSCT: hematopoietic stem cell transplantation; PEBL: protein expression blocker; r/r: relapsed/refractory; T-ALL/LBL: T-cell acute lymphoblastic leukemia / lymphoblastic lymphoma; TBI: total body irradiation; TKI: tyrosine kinase inhibitor; USA: United Sates of America; ven: venetoclax; VHR: very high risk; YA: young adult.

early phase immunotherapy trials in r/r T-ALL recommend or require consolidation with HSCT. Additionally, while viral infections have been reported following CAR-T, unmitigated T-cell aplasia has not been seen due to expansion of rare populations. Several promising therapeutics have been highlighted in this review; however there is a notable paucity of randomized-controlled trials comparing regimens. Nevertheless, with the improved ability to risk-stratify patients, the recent identification of novel targets for small molecule inhibitors and the ability to safely and effectively translate immunotherapies, it is possible we are entering a new era where almost all children with T-ALL/T-LBL are cured.

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