Precision medicine in acute lymphoblastic leukemia

Ching-Hon Pui
Departments of Oncology and Pathology, St. Jude Children’s Research Hospital, Memphis, TN 38105, USA

Abstract

The cure rate of childhood acute lymphoblastic leukemia (ALL) has exceeded 90% in some contemporary clinical trials. However, the dose intensity of conventional chemotherapy has been pushed to its limit. Further improvement in outcome will need to rely more heavily on molecular therapeutic as well as immunoand cellular-therapy approaches together with precise risk stratification. Children with ETV6-RUNX1 or hyperdiploid > 50 ALL who achieve negative minimal residual disease during early remission induction are suitable candidates for reduction in treatment. Patients with Philadelphia chromosome (Ph)-positive or Ph-like ALL with ABL-class fusion should be treated with dasatinib. BH3 profiling and other preclinical methods have identified several high-risk subtypes, such as hypodiploid, early T-cell precursor, immature T-cell, KMT2A-rearranged, Ph-positive and TCF-HLF-positive ALL, that may respond to BCL-2 inhibitor venetoclax. There are other fusions or mutations that may serve as putative targets, but effective targeted therapy has yet to be established. For other high-risk patients or poor early treatment responders who do not have targetable genetic lesions, current approaches that offer hope include blinatumomab, inotuzumab and CAR-T cell therapy for B-ALL, and daratumumab and nelarabine for T-ALL. With the expanding therapeutic armamentarium, we should start focus on rational combinations of targeted therapy with non-overlapping toxicities.

Keywords

acute lymphoblastic leukemia; molecular therapeutics; targeted therapy; tyrosine kinase inhibitors; immunotherapy; CAR T-cell therapy
Introduction
Contemporary risk-directed treatment has improved 5-year event-free survival and overall survival rates in childhood acute lymphoblastic leukemia (ALL) to over 80% and 90%, respectively, and has decreased the cumulative risk of relapse to less than 10% in many clinical trials (Table 1) [1–11]. In a recently completed St. Jude Total Therapy Study 16, the 5-year event-free survival rate was 88.2% and the 5-year cumulative risk of any relapse 6.6% among 598 evaluable patients [9] (Fig. 1). Despite the significant reduction of cumulative risk for a CNS relapse or any relapse and a corresponding increase in event-free survival, the overall survival rate (94.1%) in the Study 16 was similar to that (93.5%) in the Study 15 [11]. This outcome suggests that the intensity of conventional chemotherapy has reached its limit of tolerance and can no longer be “pushed” to obtain improved results. Thus, if we intend to boost cure rates and the quality of life of children with ALL in the coming decade, it will be important to replace toxic chemotherapy with carefully selected components of molecular therapeutics and cellular- and immunotherapy, preferably those that lack overlapping toxicity with chemotherapy [12]. This review will focus on the molecular genetic features of the major subtypes of ALL and describe recent advances in targeted therapy that promise to secure improved clinical outcomes.

Genomic landscape of acute lymphoblastic leukemia
Recent studies have refined the classification of B- and T-lineage ALL into gene expression-based subgroups, and the comprehensive integration of specific mutated genes and pathways for each subgroup has significantly improved our understanding of the disease biology. Cases can be classified based on whole transcriptome sequencing (RNA-seq); aneuploidy or other chromosomal abnormality; deregulation of known transcription factors by mutations or rearrangement; or activation of kinase alterations into at least 23 subtypes of B-ALL and 9 subtypes of T-ALL, many of which have prognostic or therapeutic implications [13–15]. However, heterogeneity still exists in treatment response among patients with the same genetic subtypes due to cooperative mutations, germline genetic variants, and other host or environmental factors [16]. Thus, key genetic alterations will need to be combined with clinical variables and response to therapy (as determined by minimal residual disease (MRD) measurements) to avoid over- or under-treatment. In this regard, the prognostic and therapeutic relevance of current approaches to genetic classification of T-ALL remains tenuous, even in the context of MRD-stratified therapy, so that most T-ALL patients still require intensive chemotherapy for cure [12].

Reduced dose intensity of treatment for patients with favorable genotypes and excellent early treatment responses
Contemporary protocols allow the reduction of treatment dose intensity to improve the quality of life for low-risk patients while maintaining their cure high rates. In the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP) and Berlin-Frankfurt-Münster (BFM) ALL 2000 protocol, patients 1 to 17 years old with standard-risk B-ALL, defined by the absence of high-risk genetic features (BCR-ABL1, KMT2A-AFF1) and the lack MRD disease (i.e., level < 1 × 10^{-4}) on days 33 and 78 from the start of remission induction treatment, were randomized to receive standard or reduced delayed intensification.
treatment [17]. This modification resulted in a poorer overall 8-year disease-free survival (89.2% ± 1.3% vs. 92.3% ± 1.2%) and overall survival (96.1% ± 0.8% and 98.0% ± 0.6%) except for the patients with ETV6-RUNX1-positive ALL or ages of 1 to 6 years who fared equally well in both treatment arms. This study shows that treatment reduction in this context is only feasible in specific subgroups of patients with standard-risk ALL.

In St. Jude Total Therapy Study 15, only low-risk B-ALL patients with ETV6-RUNX1-positive or hyperdiploid > 50 ALL and negative MRD (< 1 × 10^-4) on day 19 of remission induction had a low cumulative risk of relapse (1.9% and 3.8%, respectively) as compared to an unacceptably high cumulative risk of relapse (9.5%) in low-risk (i.e., NCI standard-risk B-ALL) patients with other genotypes and negative MRD on day 19 [18]. In a Children’s Oncology Group study, the 56 patients with NCI standard-risk B-ALL and undetectable MRD by high-throughput sequencing (< 10^-5) at the end of remission induction had an excellent 5-year event-free survival of 98.1% and an overall survival of 100% [19]. Hence, only two subgroups appear to be suitable candidates for reduced treatment: (1) B-ALL patients with a favorable genotype (ETV6-RUNX1 positivity or hyperdiploidy > 50) who achieve an early negative MRD status (10^-4) by conventional methods or (2) other NCI standard-risk B-ALL patients with negative MRD by high-throughput sequencing (< 10^-5) at the end of remission induction.

Two other newly identified genotypes of B-ALL, DUX4-rearranged (with overexpression of DUX4 and transcriptional deregulation of ERG) and ETV6-RUNX1like (with gene expression profile similar to that of ETV6-RUNX1-positive ALL and coexisting ETV6 and IKZF1 alterations), appeared to have favorable prognosis in retrospective studies [14,20,21]. However, because small numbers of patients were studied, their favorable prognosis required confirmation. At present, there are no reliable biomarkers that could be used to identify subsets of T-ALL patients who might benefit reduced-intensity chemotherapy [9,12,22].

**High-risk genetic subtypes that benefit from targeted therapy**

**Philadelphia chromosome-positive ALL**—Although addition of imatinib, the first-generation ABL1 tyrosine kinase inhibitor, to conventional treatment has improved outcome in children with Philadelphia chromosome (BCR-ABL1)-positive ALL [23–25], refractory or relapsed disease remains a difficult problem in these cases. To overcome resistance-inducing ABL1 kinase domain mutations, dasatinib and nilotinib, two second-generation tyrosine kinase inhibitors, were developed [26]. Dasatinib, the more commonly used dual ABL and SRC kinase inhibitor, can cross the blood-brain barrier [27].

Two nonrandomized clinical trials suggested that dasatinib (at 60 mg/m^2 per day) can secure results comparable to those achieved with imatinib, with a lower proportion of dasatinib-treated patients undergoing allogeneic hematopoietic cell transplantation or cranial irradiation than imatinib-treated patients [28,29]. However, because of the use of historical controls and the differences in the proportion of patients undergoing transplantation and cranial irradiation in imatinib- vs. dasatinib-treated patients, the relative efficacy of these two agents remains uncertain. Moreover, despite transplantation in 32% and 14% of the patients and prophylactic cranial irradiation for patients with a CNS3 status, 4 of 60 and
4 of 106 dasatinib-treated patients developed CNS relapse in the two studies, respectively [28,29].

In St. Jude Total Therapy Study 16, the 15 Philadelphia chromosome-positive ALL patients treated with dasatinib (80 mg/m\(^2\) per day) had an excellent 5-year event-free survival rate of 71% and none developed CNS relapse, despite total omission of cranial irradiation and transplantation limited to 1 patient [9]. The Chinese Children’s Cancer Group recently conducted the first randomized study comparing the efficacy of imatinib (300 mg/m\(^2\) per day) with that of dasatinib (80 mg/m\(^2\) per day) in children with Philadelphia chromosome-positive ALL [30]. By the study design, no patients received prophylactic cranial irradiation and only 2% of the patients with MRD \(\geq 1\%\) after remission induction received allogeneic transplantation. The dasatinib-treated patients had a significantly better event-free survival and overall survival than the imatinib-treated patients and only one of 92 dasatinib-treated patients developed CNS relapse. These findings suggest that dasatinib administered at 80 mg/m\(^2\) per day improved outcome by achieving optimal therapeutic level both systemically and in the CNS.

Ponatinib is the most potent third-generation of ABL1 class tyrosine kinase inhibitors and is active against cases with mutated \(ABL1\), including Thr315Ile [26]. A recent adult study incorporating this drug achieved an excellent 3-year event-free survival of 70%, with only 20% of the patients undergoing allogeneic transplantation [31]. Investigation of this drug in the pediatric population is warranted.

**Philadelphia chromosome-like ALL**—Philadelphia chromosome-like B-ALL, characterized by an activated kinase gene expression profile resembling that of Philadelphia chromosome-positive ALL with a high frequency of IKZF1 alterations but lacking \(BCR-ABL1\) fusion, occurs in approximately 12% of childhood B-ALL cases [32]. However, this genotype is heterogeneous and has a wide range of genetic alterations, many of which respond to different tyrosine kinase or signal pathway inhibitors [32–34]. Approximately half of these patients have \(CRLF2\) (cytokine receptor-like factor 2) rearrangements, leading to activation of \(PI3K/AKT/mTOR\) and \(JAK-STAT\) signaling, especially in older patients and in Native American and Hispanic or Latino populations [35]. Among childhood and adolescent patients with \(CRLF2\) rearrangement, approximately half have concomitant \(JAK2\) or \(JAK1\) mutations, which may respond to \(JAK-STAT\) inhibitors such as ruxolitinib [32–35].

Among the other half of patients with Philadelphia chromosome-like ALL lacking \(CRLF2\) rearrangements, 15%–20% have rearrangements in \(ABL1, ABL2, CSF1R,\) or platelet-derived growth factor receptor (\(PDGFR\)) \(\alpha\) or \(\beta\) and would likely respond to ABL-class tyrosine kinase inhibitors. Another 10%–15% of patients have lesions that activate JAK–STAT signaling, including \(JAK2\) fusions or truncating rearrangements in erythropoietin receptor [32–35]. There are other uncommon kinase fusion events involving \(NTRK3, PTK2B, TYK2, FLT3, FGFR1,\) and \(BLNK,\) which have been responsive to TRK inhibitor, FAK inhibitor, TYK2 inhibitor, FLT3 inhibitor, sorafenib/dasatinib, and SYK/MEKi, respectively, in preclinical settings [32,33].
Although a high proportion of Philadelphia chromosome-like ALL cases have an unfavorable outcome, approximately 40% of the childhood cases are highly curable even with low-intensity chemotherapy. This subgroup can be readily identified with negative MRD status upon completion of remission induction [36]. Hence, it is mandatory to measure MRD levels to avoid overtreatment of these cases.

**Hypodiploid ALL**—Hypodiploid ALL, found in 2% to 3% of childhood ALL cases, is also a heterogeneous disease, comprising several subgroups with different biologic and prognostic features [37]. Near-haploid ALL (25–29 chromosomes) is characterized by genetic alterations affecting RAS signaling and receptor tyrosine kinase signaling, and a high frequency of IKZF3 alterations [37]. Low-hypodiploid cases (33–39 chromosomes) often have alterations in TP53, IKZF2, and RB1. Alterations in TP53 have been identified in as many as 90% of patients with low hypodiploid ALL, with approximately 50% of these cases having germline TP53 alterations [37], which are associated with inferior event-free survival and overall survival as well as an increased risk of developing secondary cancer [38], regardless of ploidy status. Thus, all patients with low hypodiploid ALL should be tested for a germline TP53 pathogenic variant (e.g., Li-Fraumeni syndrome, a well-known hereditary cancer predisposition syndrome [39]).

A recent multinational study of 306 cases further characterized the clinical and biologic prognostic hallmarks of hypodiploid ALL [40]. The results showed that despite contemporary treatment, patients with hypodiploid ALL continue to have poor overall outcome with an 8-year survival rate for the entire cohort of only 57.5%. It also demonstrated that hypodiploidy may accompany specific driver genetic abnormalities with known prognostic significance, such as BCR-ABL1, TCF3-PBX1, ETV6-RUNX1, and KMT2A rearrangements. These cases should be treated according to their driver mutations and MRD level after remission induction because the treatment outcomes closely reflect each specific driver mutation [40]. In this regard, only one of 18 hypodiploid patients with concomitant ETV6-RUNX1 relapsed, while the remaining 17 patients were alive in long-term remission. Three independent favorable prognostic factors were identified: (1) negative MRD at the end of remission induction, (2) high hypodiploidy with 44 chromosomes, and (3) treatment in MRD-stratified protocols. Importantly, allogeneic transplantation failed to improve outcome compared with chemotherapy alone, especially for patients who achieved a negative MRD status after remission induction, a finding confirmed by a Children’s Oncology Group study that treated patients during the same time period [41]. A recent preclinical study identified Bcl-2 as a key therapeutic target and demonstrated the efficacy of a selective Bcl-2 inhibitor, venetoclax, in hypodiploid ALL, providing a promising treatment strategy to improve outcome in this disease [42].

**Other genotypes that may be targetable by venetoclax**

Deregulated cell death pathways contribute to treatment failure in many cancers, including certain subtypes of ALL. Intrinsic apoptotic signaling is regulated by proapoptotic BCL-2 homology domain 3 (BH3) proteins that trigger apoptotic cell death and by antiapoptotic molecules including BCL-2 that counter-regulate apoptosis induction. A treatment strategy of inhibiting antiapoptotic regulators led to the development of the BCL-2 inhibitor
venetoclax. A functional assay, BH3 profiling, measured the state of the mitochondrial apoptosis pathway in cells, and was developed to predict types of cancers that would respond to this class of drugs [43]. BH3 profiling and other preclinical methods have identified a number of high-risk leukemias, including early T cell precursor ALL [44], immature T-ALL [45], KMT2A (MLL)-rearranged ALL [46,47] and Philadelphia chromosome-positive ALL [48,49] as well as TCF-HLF-positive ALL, the most aggressive form of ALL [50], all of which are Bcl-2 dependent and sensitive in vitro and in vivo to treatment with venetoclax. Clinical trials are warranted to determine if venetoclax can improve outcome in these high-risk subtypes of leukemia.

**MEF2D-rearranged ALL**—Rearrangements between MEF2D (myocyte enhancer factor 2D) and various genes (BCL9, CSF1R, DAZAPI, HNRPUL1, HNRNPH1, SS18, FOXJ2) occurred in approximately 2% to 3.5% of patients with a cytoplasmic μ chain pre-B immunophenotype, older presenting age (median 12 years) and poor outcome (5-year survival ranging between 30% to 70%) [14,51,52]. In a study of relapsed ALL, MEF2D-BCL9 fusion was found in 4 of 59 relapsed or refractory ALL patients who had older age (10 to 13 years), very early relapse (8 to 15 months from diagnosis), and very poor outcome (0% survival) [53]. The rearrangements resulted in upregulation of pre-B cell receptor signaling molecules, downregulation of JAK-STAT signaling pathway, enhanced MEF2D transcriptional activity and activation of HDAC9 expression, with sensitivity to histone deacetylase inhibitors such as panobinostat [14,51,52]. Studies are needed to assess the heterogeneity of treatment responses among patients with different fusion partners and whether these cases respond to treatment with histone deacetylase inhibitors.

**PAX5-driven B-ALL**—Recent integrated genomic analyses identified two subtypes of B-ALL with frequent alterations of the Blymphoid transcription factor PAX5 [13,54]. One, designated PAX5alt, has diverse alterations (mutations, intragenic amplifications or rearrangement) of the gene, while the other, PAX5P80R, has PAXp.Pro80Arg and biallelic PAX5 alterations. In one study, patients with either set of changes had a higher median age (22 and 15.4 years vs.13 years for the total patient cohort) and a lower MRD level at the end of induction (7.2% and 29.4% vs.37.8% for the total cohort). Not surprisingly, pediatric patients had intermediate treatment outcomes: 5-year event-free survival rates of 75% ± 14.2% and 71.5% ± 7%, respectively [13]. To date, no molecularly targeted therapy has been identified.

**Mixed-lineage acute leukemias**

Recent comprehensive genomic and immunophenotypic analyses have provided important insights into the biology and treatment response among immunophenotypically defined subtypes of acute leukemia expressing both lymphoid and myeloid markers, which account for 2% to 3% of childhood acute leukemias [55,56]. These so-called mixed-phenotype acute leukemias can be broadly classified into B-myeloid and T-myeloid subtypes. KMT2A-rearranged, Philadelphia chromosome-positive and ZNF384-rearranged leukemias are the most common genotypes among B-myeloid leukemia, and biallelic WT1 alterations are common in the T-myeloid subtype, which shares genomic features such as RAS and JAK–STAT pathway mutations with early T cell precursor ALL [55]. Overall, B-myeloid and
T-myeloid leukemias have similar treatment outcomes except for KMT2A-rearranged cases, which typically have a very poor prognosis [47]. In a retrospective multinational study, lymphoid-directed therapy was superior to myeloid-directed therapy for most pediatric patients with mixed-phenotype acute leukemias, except for a minority of patients with CD19-negative leukemia, who benefitted from myeloid-directed therapy [56].

**Leukemias without available molecular targeted therapy**

A substantial proportion of high-risk ALL patients with poor early treatment responses, for example, those with iAMP21 [57], do not have targetable genetic lesions or effective molecular therapeutics available. Current treatment approaches besides intensive chemotherapy that offer hope for this subgroup are immunotherapy and adoptive cell therapy. Blinatumomab, a bispecific T cell engager antibody, by binding to CD3 on the surface of T cells and CD19 on leukemia cells, initiates T cell receptor-mediated activation and killing of CD19-positive B-ALL [58]. It has been shown to improve outcome in multiple studies of adults with refractory, relapsed and newly diagnosed Philadelphia chromosome-negative or positive ALL [58]. In fact, the combination of ABL tyrosine kinase inhibitor and blinatumomab may synergistically improve the outcome of patients with Philadelphia chromosome positive ALL [59]. Blinatumomab was recently approved for pediatric patients with relapsed or refractory ALL after a phase I/II trial showing 39% complete remission rate with 52% of the responders achieving an MRD negative status within the first two cycles of treatment [60]. While blinatumomab is generally well-tolerated, it has been associated with severe and potentially life-threatening adverse events, including cytokine release syndrome and neurotoxicity, which can occur simultaneously or independently [61]. The rate of cytokine release syndrome could be reduced by a debulking sequential combination approach [58]. An ongoing adult study is investigating the combination of immune checkpoint blockade with blinatumomab treatment to enhance T cell activation and hence augment the activity of the antibody (NCT03160079) [59].

The anti-CD22/calicheamicin conjugate (inotuzumab ozogamicin) is an effective FDA-approved agent in the treatment of adults with relapsed ALL [62]. Among 51 children with relapsed or refractory ALL treated with inotuzumab ozogamicin in a compassionate-use program, complete remission was achieved in 67% of the patients with overt marrow disease, and the majority (71%) of the responders were negative for MRD [63]. The treatment was well tolerated; sinusoidal obstruction syndrome was not observed in any patients during treatment but developed in 11 of 21 patients (52%) after hematopoietic cell transplantation. The combination of non-intensive chemotherapy and blinatumomab plus inotuzumab have been evaluated in adults with ALL in first relapse with encouraging results [64]; similar studies have yet to be conducted in children.

The most effective FDA-approved cellular therapy is the use of CD19-specific chimeric antigen receptor (CAR) T cells containing a 4–1BB (CD137) domain to provide a costimulatory signal. In a recent global study of 75 patients with relapsed or refractory B-ALL treated with tisagenlecleucel (CD19-targeted CAR T cells), the overall complete remission rate within 3 months was 81%, and the 12-month event-free and overall survival rates were 50% and 76%, respectively [65]. The cytokine release syndrome occurred within
a median time to onset of 3 days (range, 1 to 22) in 77% of the patients, of whom 47% were admitted to intensive care unit and 48% of whom required tocilizumab. Neurologic adverse events (encephalopathy, confusion, delirium, tremor, agitation, somnolence and seizure) occurred in 40% of the patients within 8 weeks after infusion. Of the 22 relapsed cases, 1 had CD19+ recurrence, 15 had CD19− recurrence (3 with concomitant CD19+ blasts) and 6 had an unknown CD19 status. Interestingly, CAR-T cells can eradicate leukemia cells in central nervous system and testes [66,67], sparing patients with extramedullary disease from receiving local irradiation.

In a recent report of a phase 1 trial testing a CD22-targeted CAR-T cell therapy in 21 children and adults, including 17 who were previously treated with CD19-directed immunotherapy, dose-dependent antileukemic activity was observed, with complete remission achieved in 11 of the 15 patients receiving ≥1 ± 10^6 CD22-CART cells per kg of body weight, including all 5 patients with CD19dim or CD19− B-ALL [68]. However, the median remission duration was only 6 months. Relapses were associated with a diminished CD22 site density that likely permitted CD22+ cell escape from killing by the CD22-CAR-T cells. Thus, antigen escape is the primary cause of relapse in the majority of patients treated with either CD19- or CD22-targeted CAR-T cell therapy. These findings strongly support current research to develop simultaneous CD19- and CD22-targeting with CAR-T cells to disallow the opportunity and time for sequential loss of both antigens [69]. Although immunotherapy and adoptive cellular therapy have been used in the relapse or refractory setting, they are being brought forward to newly diagnosed B-ALL patients and promise to improve outcome of these patients.

For T-ALL patients, curative therapeutic options for relapsed or refractory disease beyond allogeneic transplantation are lacking. Translating CAR-T cell therapies into the setting of T-ALL have not yet been successful, and there is a theoretical risk of so-called fratricide by T cell-targeted clones because of the shared expression of target antigens between CAR-T cells and T-leukemia cells, and the risk of severe life-threatening immunodeficiency from elimination of normal T lymphocytes [70,71]. Recently, fratricide-resistant CD7, CD5, and CD1a-targeted CAR-T cells with specific cytotoxicity in vitro and antileukemic activity in vivo in xenograft models [72,73], and universal allo-tolerant off-the-shelf CAR-T cells generated by genomic editing [74,75] have been developed in an attempt to overcome those limitations but have yet to be tested in a clinical setting.

Nelarabine is the only drug approved specifically for relapsed T-ALL. In a recent Children’s Oncology Group trial (AALL0434) for T-ALL, in which all intermediate- or high-risk patients received cranial irradiation, those randomized to receive nelarabine had an excellent treatment outcome [76]. The 4-year disease-free survival was 88.9% for patients who received nelarabine, compared with 83.3% for those treated without this agent. However, this improvement was noted only in the subset of patients randomized to receive high-dose methotrexate and not in the other subset randomized to receive escalating doses of methotrexate. Thus, additional studies are needed to determine the true efficacy of nelarabine. Among several antibodies being evaluated, the anti-CD38 monoclonal antibody daratumumab appears promising, as this target is overexpressed on T-ALL cells but
expressed in very low levels on normal lymphoid and myeloid cells, and the antibody was very effective against T-ALL in human xenograft models [77].

**Conclusions**

With improved genomic sequencing and the development of novel molecular, immunological and cellular therapy, we are now entering an exciting era of precision medicine for ALL. Replacing toxic chemotherapy with precisely targeted therapy promises to improve not only the cure rate of this disease, but also the quality of life of patients. Table 2 summarizes some of the potential therapeutic intervention for various subtypes of ALL. Similar to conventional chemotherapy, we should focus on rational combinations of targeted therapies with non-overlapping toxicities, allowing the agents to act synergistically to kill leukemia cells while sparing normal tissues from excessive toxicity. For example, while venetoclax by itself has limited activity against T-ALL, with the exception of early T-cell precursor or immature T cell ALL [44,45], the combination of venetoclax and navitoclax, a Bcl-2 inhibitor that also inhibits Bcl-X<sub>L</sub> and Bcl-w, may achieve effective activity against T-ALL while sparing patients from profound navitoclax-induced thrombocytopenia [78]. This hypothesis is being tested in a study (NCT3181126) for children ≥4 years old and adults with refractory or relapsed ALL.

**Acknowledgements**

This work is supported in part by the US National Institute of Health (Nos. P30CA021765, P50GM115279, and R01CA036401) and American Lebanese Syrian Associated Charities (ALSAC).

**References**

1. Möricke A, Zimmermann M, Valsecchi MG, Stanulla M, Biondi A, Mann G, Locatelli F, Cazzaniga G, Niggli F, Aricò M, Bartram CR, Attarbaschi A, Silvestri D, Beier R, Basso G, Ratei R, Kulozik AE, Lo Nigro L, Kremens B, Greiner J, Harbott J, Caruso R, von Stackelberg A, Barisone E, Rössig C, Conter V, Schrappe M. Dexamethasone vs prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000. Blood 2016; 127(17): 2101–2112 [PubMed: 26888258]

2. Escherich G, Zimmermann M, Janka-Schaub, CoALL study group. Doxorubicin or daunorubicin given upfront in a therapeutic window are equally effective in children with newly diagnosed acute lymphoblastic leukemia. A randomized comparison in trial CoALL 07–03. Pediatr Blood Cancer 2013; 60(2): 254–257 [PubMed: 22948968]

3. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, Reaman GH, Carroll WL. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children’s oncology group. J Clin Oncol 2012; 30(14): 1663–1669 [PubMed: 22412151]

4. Pieters R, de Groot-Kruiseman H, Van der Velden V, Fiocco M, vanden Berg H, de Bont E, Egeler RM, Hoogerbrugge P, Kaspers G, Van der Schoot E, De Haas V, Van Dongen J. Successful therapy reduction and intensification for childhood acute lymphoblastic leukemia based on minimal residual disease monitoring: Study ALL10 From the Dutch Childhood Oncology Group. J Clin Oncol 2016; 34(22): 2591–2601 [PubMed: 27269950]

5. Vrooman LM, Blonquist TM, Harris MH, Stevenson KE, Place AE, Hunt SK, O’Brien JE, Asselin BL, Athale UH, Clavell LA, Cole PD, Kelly KM, Laverdiere C, Leclere JM, Michon B, Schorin MA, Sulis ML, Welch JG, Neuberg DS, Sallan SE, Silverman LB. Refining risk classification in childhood B acute lymphoblastic leukemia: results of DFCI ALL Consortium Protocol 05–001. Blood Adv 2018; 2(12): 1449–1458 [PubMed: 29941458]
6. Domenech C, Suciu S, De Moerloose B, Mazingue F, Plat G, Ferster A, Uyttebroeck A, Sirvent N, Lutz P, Yakouben K, Munzer M, Röhrlich P, Plantaz D, Millot F, Philippet P, Dastugue N, Girard S, Cavé H, Benoit Y, Bertrandfor Y, Children’s Leukemia Group (CLG) of European Organisation for Research and Treatment of Cancer (EORTC). Dexamethasone (6 mg/m²/day) and prednisolone (60 mg/m²/day) were equally effective as induction therapy for childhood acute lymphoblastic leukemia in the EORTC CLG 58951 randomized trial. Haematologica 2014; 99(7): 1220–1227 [PubMed: 24727815]

7. Vora A, Goulden N, Mitchell C, Hancock J, Hough R, Rowntree C, Moorman AV, Wade R. Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. Lancet Oncol 2014; 15(8): 809–818

8. Toft N, Birgens H, Abrahamsson J, Grīškevičius L, Hallbök H, Heyman M, Klausen TW, Jönsson OG, Palk K, Pruunsild K, Vaitkeviciene G, Vettenranta K, Åsberg A, Frandsen TL, Madsen HO, Norén-Nyström U, Schmiegelow K. Results of NOPHO ALL2008 treatment for patients aged 1 – 45 years with acute lymphoblastic leukaemia. Leukemia 2018; 32(3): 606–615 [PubMed: 28819280]

9. Jeha S, Pei D, Choi J, Cheng C, Sandlund JT, Coustan-Smith E, Campana D, Inaba H, Rubnitz JE, Ribeiro RC, Gruber TA, Raimondi SC, Khan RB, Yang JJ, Mullighan CG, Downing JR, Evans WE, Relling MV, Pui CH. Improved CNS control of childhood acute lymphoblastic leukemia without cranial irradiation: St Jude Total Therapy Study 16. J Clin Oncol 2019; 37(35): 3377–3391 [PubMed: 31657981]

10. Liu HC, Yeh TC, Hou JY, Chen KH, Huang TH, Chang CY, LiangDC. Triple intrathecal therapy alone with omission of cranial radiation in children with acute lymphoblastic leukemia. J Clin Oncol 2014; 32(17): 1825–1829 [PubMed: 24821882]

11. Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, Ribeiro RC, Rubnitz JE, Raimondi SC, Onciu M, Coustan-Smith E, Kun LE, Jeha S, Cheng C, Howard SC, Simmons V, Bayles A, Metzger ML, Boyett JM, Leung W, Handgretinger R, Downing JR, Evans WE, Relling MV. Treating childhood acute lymphoblastic leukemia without cranial irradiation: N Engl J Med 2009; 360(26): 2730–2741 [PubMed: 19553647]

12. Teachey DT, Pui CH. Comparative features and outcomes between paediatric T-cell and B-cell acute lymphoblastic leukaemia. Lancet Oncol 2019; 20(3): e142–e154 [PubMed: 30842058]

13. Gu Z, Churchman ML, Roberts KG, Moore I, Zhou X, Nakitandwe J, Hagiwara K, Pelletier S, Gingras S, Berns H, Payne-Turner D, Hill A, Iacobucci I, Shi L, Pounds S, Cheng C, Pei D, Qu C, Newman S, Devidas M, Dai Y, Reshmi SC, Gastier-Foster J, Raetz EA, Borowitz MJ, Wood BL, Carroll WL, Zweidler-McKay PA, Rabin KR, Mattano LA, Maloney KW, Rambaldi A, Spinelli O, Radich JP, Minden MD, Rowe JM, Sizov MR, Tallman MS, Racevskis J, Zhang Y, Bhatia R, Kohlschmidt J, Mrózek K, Bloomfield CD, Kornblau S, Kantarjian HM, Konopleva M, Evans WE, Jeha S, Pui CH, Yang J, Paietta E, Downing JR, Relling MV, Zhang J, Loh ML, Hunger SP, Mullighan CG. PAX5-driven subtypes of B-progenitor acute lymphoblastic leukemia. Nat Genet 2019; 51(2): 296–307 [PubMed: 30643249]

14. Liu YF, Wang BY, Zhang WN, Huang JY, Li BS, Zhang M, Jiang L, Li JJ, Wang MJ, Dai YJ, Zhang ZG, Wang Q, Kong J, Chen B, Zhu YM, Weng XQ, Shen ZX, Li JM, Wang J, Yan XJ, Li Y, Liang YM, Liu L, Chen QX, Zhang WG, Yan JS, Hu JD, Shen SH, Chen J, Gu LJ, Pei D, Li Y, Wu G, Zhou X, Ren RB, Cheng C, Yang JJ, Wang KK, Wang SY, Zhang J, Mi JQ, Pui CH, Tang JY, Chen Z, Chen SJ. Genomic profiling of adult and pediatric B-cell acute lymphoblastic leukemia. EBioMedicine 2016; 8: 173–183 [PubMed: 27428428]

15. Liu Y, Easton J, Shao Y, Maciaszek J, Wang Z, Wilkinson MR, McCastlain K, Edmonson M, Pounds SB, Shi L, Zhou X, Ma X, Sioson E, Li Y, Ruch M, Gupta P, Pei D, Cheng C, Smith MA, Auvil JG, Gerhard BS, Relling MV, Winick NJ, Carroll AJ, Heerema NA, Raetz E, Devidas M, Willman CL, Harvey RC, Carroll WL, Dunsmore KP, Winter SS, Wood BL, Sorrentino BP, Downing JR, Loh ML, Hunger SP, Zhang J, Mullighan CG. The genomic landscape of pediatric and young adult T-lineage acute lymphoblastic leukemia. Nat Genet 2017; 49(8): 1211–1218 [PubMed: 28671688]

16. Pui CH, Nichols KE, Yang JJ. Somatic and germline genomics in paediatric acute lymphoblastic leukaemia. Nat Rev Clin Oncol 2019; 16(4): 227–240 [PubMed: 30546053]
17. Schrappe M, Bleckmann K, Zimmermann M, Biondi A, Möricker A, Locatelli F, Cario G, Rizzari C, Attarbaschi A, Valsecchi MG, Bartram CR, Barisone E, Niggli F, Niemeyer C, Testi AM, Mann G, Ziino O, Schäfer B, Panzer-Grümayer R, Beier R, Parasole R, Göhring G, Ludwig WD, Casale F, Schlegel PG, Basso G, Conter V. Reduced-intensity delayed intensification in standard-risk pediatric acute lymphoblastic leukemia defined by undetectable minimal residual disease: results of an international randomized trial (AIEOP-BFM ALL 2000). J Clin Oncol 2018; 36(3): 244–253 [PubMed: 29148893]

18. Pui CH, Pei D, Raimondi SC, Coustan-Smith E, Jeha S, Cheng C, Bowman WP, Sandlund JT, Ribeiro JE, Rubnitz JE, Inaba H, Gruber TA, Leung WH, Yang JJ, Downing JR, Evans WE, Relling MV, Campana D. Clinical impact of minimal residual disease in children with different subtypes of acute lymphoblastic leukemia treated with response-adapted therapy. Leukemia 2017; 31(2): 333–339 [PubMed: 27560110]

19. Wood B, Wu D, Crossley B, Dai Y, Williamson D, Gawad C, Borowitz MJ, Devidas M, Maloney KW, Larsen E, Winick N, Raetz E, Carroll WL, Hunger SP, Loh ML, Robins H, Kirsch I. Measurable residual disease detection by high-throughput sequencing improves risk stratification for pediatric B-ALL. Blood 2018; 131(12): 1350–1359 [PubMed: 29284596]

20. Zhang J, McCastlain K, Yoshihara H, Xu B, Chang Y, Churchman ML, Wu G, Li Y, Wei L, Iacobucci I, Liu Y, Qu C, Wen J, Edmonson M, Payne-Turner D, Kaufmann KB, Takayanagi SI, Wienholds E, Waanders E, Ntziachristsos P, Bakogianni S, Wang J, Aifantis I, Roberts KG, Ma J, Song G, Easton J, Mulder HL, Chen X, Newman S, Ma X, Rusch M, Gupta P, Boggs K, Vadodaria B, Dalton J, Liu Y, Valentine ML, Ding L, Lu C, Fulton RS, Fulton L, Tabib Y, Ochoa K, Devidas M, Pei D, Cheng C, Yang J, Evans WE, Relling MV, Pui CH, Jeha S, Harvey RC, Chen IL, Willman CL, Marcucci G, Bloomfield CD, Kohlschmidt J, Mrózek K, Paietta E, Tallman MS, Stock W, Foster MC, Racevskis J, Rowe JM, Sagner SM, Shurtleff SA, Raimondi SC, Mardis ER, Wilson RK, Dick JE, Hunger SP, Loh ML, Downing JR, Mullighan CG, St. Jude Children’s Research Hospital–Washington University Pediatric Cancer Genome Project. Deregulation of DUX4 and ERG in acute lymphoblastic leukemia. Nat Genet 2016; 48(12): 1481–1489 [PubMed: 27776115]

21. Lilljebjörn H, Henningsson R, Hyrenius-Wittsten A, Olsson L, Orsmark-Pietras C, von Pallfy S, Asmyr M, Rissler M, Schrappe M, Cario G, Castor A, Prönk CJ, Behrendtz M, Mitelman F, Johansson B, Paulsson K, Andersson AK, Fontes M, Fioretos T. Identification of ETV6-RUNX1-like and DUX4-rearranged subtypes in paediatric B-cell precursor acute lymphoblastic leukaemia. Nat Commun 2016; 7(1): 11790 [PubMed: 27265895]

22. Winter SS, Dunsmore KP, Devidas M, Wood BL, Esiahvili N, Chen Z, Eisenberg N, Briegel N, Hayashi RJ, Gastier-Foster JM, Carroll AJ, Heerema NA, Asselin BL, Gaynon PS, Borowitz MJ, Loh ML, Rabin KR, Raetz EA, Zweidler-Mckay PA, Winick NJ, Carroll WL, Hunger SP. Improved survival for children and young adults with T-lineage acute lymphoblastic leukemia: results from the Children’s Oncology Group AALL0434 Methotrexate Randomization. J Clin Oncol 2018; 36(29): 2926–2934 [PubMed: 30138085]

23. Schultz KR, Carroll A, Heerema NA, Bowman WP, Aledo A, Slayton WB, Sather H, Devidas M, Zheng HW, Davies SM, Gaynon PS, Trigg M, Rutledge R, Jorstad D, Winick N, Borowitz MJ, Hunger SP, Carroll WL, Camitta B, Children’s Oncology Group. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children’s Oncology Group study AALL0433. Leukemia 2018; 30(9): 1752–1757 [PubMed: 29730511]

24. Biondi A, Schrappe M, De Lorenzo P, Castor A, Lucchini G, Gandemer V, Pieters R, Stary J, Escherich G, Campbell M, Li CK, Vora A, Aričo M, Rötgers S, Saha V, Valsecchi MG. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. Lancet Oncol 2012; 13(9): 936–945 [PubMed: 22898679]

25. Biondi A, Gandemer V, De Lorenzo P, Cario G, Campbell M, Castor A, Pieters R, Baruchel A, Vora A, Leoni V, Stary J, Escherich G, Li CK, Cazzaniga G, Cavé H, Bradl J, Conter V, Saha V, Schrappe M, Grazia Valsecchi M. Imatinib treatment of paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia (EsPhALL2010): a prospective, intergroup, open-label, single-arm clinical trial. Lancet Haematol 2018; 5(12): e641–e652 [PubMed: 30501871]
26. Short NJ, Kantarjian H, Pui CH, Goldstone A, Jabbour E. SOHO State of the Art Update and Next Questions: Philadelphia chromosome-positive acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk 2018; 18(7): 439–446 [PubMed: 29853276]

27. Porkka K, Koskenvesa P, Lundán T, Rimpiläinen J, Mustjoki S, Smykla R, Wild R, Luo R, Arman M, Brethon B, Eeckersels L, Hjorth-Hansen H, Högland M, Klamova H, Knutsen H, Parikh S, Raffoux E, Gruber F, Brito-Babapulle F, Dombret H, Duarte RF, Elonen E, Paquette R, Zwaan CM, Lee FY. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. Blood 2008; 112(4): 1005–1012 [PubMed: 18477770]

28. Slayton WB, Schultz KR, Kairalla JA, Devidas M, Mi X, Pulsipher MA, Chang BH, Mullighan C, Iacobucci I, Silverman LB, Borowitz MJ, Carroll AJ, Heerema NA, Gastier-Foster JM, Wood BL, Mizrahy SL, Merchant T, Brown VI, Siegel L, Siegel MJ, Raetz EA, Winick NJ, Loh ML, Carroll WL, Hunger SP. Dasatinib plus intensive chemotherapy in children, adolescents, and young adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: results of Children’s Oncology Group Trial AALL0622. J Clin Oncol 2018; 36(22): 2306–2314 [PubMed: 29812996]

29. Hunger SP, Saha V, Devidas M, et al. CA180–372: An international collaborative phase 2 trial of dasatinib and chemotherapy in pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph⁺ ALL). Blood 2017; 130 (Suppl 1): 98 [PubMed: 28705853]

30. Shen S, Chen X, Cai J, Yu J, Gao J, Hu S, Zhai X, Liang C, Ju X, Jiang H, Jin R, Wu X, Wang N, Tian X, Pan K, Jiang H, Sun L, Fang Y, Li CK, Hu Q, Yang M, Zhu Y, Zhang H, Li C, Pei D, Jeha S, Yang JJJ, Cheng C, Tang J, Zhu X, Pui CH. Effect of dasatinib vs imatinib in the treatment of pediatric Philadelphia chromosomespositive acute lymphoblastic leukemia: a randomized clinical trial. JAMA Oncol 2020; 6(3): 358–366 [PubMed: 31944221]

31. Jabbour E, Short NJ, Ravandi F, Huang X, Daver N, DiNardo CD, Konopleva M, Pemmaraju N, Wierda W, Garcia-Manero G, Sasaki K, Cortes J, Garris R, Khoury JD, Jorgensen J, Jain N, Alvarez J, O'Brien S, Kantarjian H. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. Lancet Haematol 2018; 5(12): e618–e627 [PubMed: 30501869]

32. Pui CH, Roberts KG, Yang JJ, Mullighan CG. Philadelphia chromosome-like acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk 2017; 17(8): 464–470 [PubMed: 28842136]

33. Roberts KG, Reshmi SC, Harvey RC, Chen IM, Patel K, Stonerock E, Jenkins H, Dai Y, Valentine M, Gu Z, Zhao Y, Zhang J, Payne-Turner D, Devidas M, Heerema NA, Carroll AJ, Raetz EA, Borowitz MJ, Wood BL, Mattano LA Jr, Maloney KW, Carroll WL, Loh ML, Willman CL, Gastier-Foster JM, Mullighan CG, Hunger SP. Genomic and outcome analyses of Ph-like ALL in NCI standard-risk patients: a report from the Children’s Oncology Group. Blood 2018; 132(8): 815–824 [PubMed: 29997224]

34. Boer JM, Steeghs EM, Marchante JR, Boeree A, Beaudoin JJ, Beverloo HB, Kuiper RP, Escherich G, van der Velden VH, van der Schoot CE, de Groot-Kruseman HA, Pieters R, den Boer ML. Tyrosine kinase fusion genes in pediatric BCR-ABL1-like acute lymphoblastic leukemia. Oncotarget 2017; 8(3): 4618–4628 [PubMed: 27894077]

35. Tasian SK, Hunger SP. Genomic characterization of paediatric acutelymphoblastic leukaemia: an opportunity for precision medicine therapeutics. Br J Haematol 2017; 176(6): 867–882 [PubMed: 27984637]

36. Roberts KG, Pei D, Campana D, Payne-Turner D, Li Y, Cheng C, Sandlund JT, Jeha S, Easton J, Becksfort J, Zhang J, Coustan-Smith E, Raimondi SC, Leung WH, Relling MV, Evans WE, Downing JR, Mullighan CG, Pui CH. Outcomes of children with BCR-ABL1-like acute lymphoblastic leukemia treated with risk-directed therapy based on the levels of minimal residual disease. J Clin Oncol 2014; 32(27): 3012–3020 [PubMed: 25049327]

37. Holmfeldt L, Wei L, Diaz-Flores E, Walsh M, Zhang J, Ding L, Payne-Turner D, Churchman M, Andersson A, Chen SC, McCastlain K, Becksfort J, Ma J, Wu G, Patel SN, Heatley SL, Phillips LA, Song G, Easton J, Parker M, Chen X, Rusch M, Boggs K, Vadodaria B, Hedlund E, Drenberg C, Baker S, Pei D, Cheng C, Huether R, Lu C, Fulton RS, Fulton LL, Tabib Y, Dooling DJ, Ochoa...
K, Minden M, Lewis ID, To LB, Marlton P, Roberts AW, Raca G, Stock W, Neale G, Drexler HG, Dickins RA, Ellison DW, Shurtleff SA, Pui CH, Ribeiro RC, Devidas M, Carroll AJ, Heerema NA, Wood B, Borowitz MJ, Gastier-Foster JM, Raimondi SC, Mardis ER, Wilson RK, Downing JR, Hunger SP, Loh ML, Mullighan CG. The genomic landscape of hypodiploid acute lymphoblastic leukemia. Nat Genet 2013; 45(3): 242–252 [PubMed: 23334668]

38. Qian M, Cao X, Devidas M, Yang W, Cheng C, Dai Y, Carroll A, Heerema NA, Zhang H, Moriyama T, Gastier-Foster JM, Xu H, Raetz E, Larsen E, Winick N, Bowman WP, Martin PL, Mardis ER, Fulton R, Zambetti G, Borowitz M, Wood B, Nichols KE, Carroll WL, Pui CH, Mullighan CG, Evans WE, Hunger SP, Relling MV, Loh ML, Yang JJ. TP53 germline variations influence the predisposition and prognosis of B-cell acute lymphoblastic leukemia in children. J Clin Oncol 2018; 36(6): 591–599 [PubMed: 29300620]

39. Guha T, Malkin D. Inherited TP53 mutations and the Li-Fraumeni syndrome. Cold Spring Harb Perspect Med 2017; 7(4): a026187

40. Pui CH, Rebora P, Schrappe M, Attarbaschi A, Baruchel A, Cavé H, Elitzur S, Koh K, Liu HC, Paulsson K, Pieters R, Silverman LB, Stary J, Vora A, Yeoh A, Harrison CJ, Valsecchi MG, Pui Page 13

41. McNeer JL, Devidas M, Dai Y, Carroll AJ, Heerema NA, Gastier-Foster JM, Kahwash SB, Borowitz MJ, Wood BL, Larsen E, Maloney KW, Mattano L, Winick NJ, Schultz KR, Hunger SP, Carroll WL, Loh ML, Raetz EA. Hematopoietic stem-cell transplantation does not improve the poor outcome of children with hypodiploid acute lymphoblastic leukemia: a report from Children’s Oncology Group. J Clin Oncol 2019; 37(10): 780–789 [PubMed: 30742559]

42. Diaz-Flores E, Comeaux EQ, Kim KL, Melnik E, Beckman K, Davis KL, Wu K, Akutagawa J, Bridges O, Marino R, Wohlfeil M, Braun BS, Mullighan CG, Loh ML. Bcl-2 is a therapeutic target for hypodiploid B-lineage acute lymphoblastic leukemia. Cancer Res 2019; 79(9): 2339–2351 [PubMed: 30862722]

43. Seyfried F, Demir S, Hörl RL, Stirnweiß FU, Ryan J, Scheffold A, Villalobos-Ortiz M, Boldrin E, Zingegre J, Enzenmüller S, Jenni S, Tsai YC, Bornhauser B, Kraus JM, Kestler HA, Bourquin JP, Stilgenbauer S, Letai A, Debatin KM, Meyer LH. Prediction of venetoclax activity in precursor B-ALL by functional assessment of apoptosis signaling. Cell Death Dis 2019; 10(8): 571 [PubMed: 31358732]

44. Chonghaile TN, Roderick JE, Glenfield C, Ryan J, Sallan SE, Silverman LB, Loh ML, Hunger SP, Wood B, DeAngelo DJ, Stone R, Harris M, Gutierrez A, Kellilher MA, Letai A. Maturation stage of T-cell acute lymphoblastic leukemia determines BCL-2 versus BCL-XL dependence and sensitivity to ABT-199. Cancer Discov 2014; 4(9): 1074–1087 [PubMed: 24994123]

45. Peirs S, Matthijssens F, Goossens S, Van de Walle I, Ruggiero K, deBock CE, Degryse S, Canté-Barrett K, Briot D, Clappier E, Lammens T, De Moerloose B, Benoit Y, Poppe B, Meijerink JP, Cools J, Soulier J, Rabbits TH, Taghon T, Speleman F, Van Vlierberghe P. ABT-199 mediated inhibition of BCL-2 as a novel therapeutic strategy in T-cell acute lymphoblastic leukemia. Blood 2014; 124(5): 3738–3747 [PubMed: 25301704]

46. Khaw SL, Suryani S, Richardson J, Robbins A, Kurmasheva RT, Billups CA, Erickson SW, Guo Y, Houghton PJ, Smith MA, Carol H, Roberts AW, Huang DC, Lock RB. Venetoclax responses of pediatric ALL xenografts reveal sensitivity of MLL-rearranged leukemia. Blood 2016; 128(10): 1382–1395 [PubMed: 27343252]

47. Benito JM, Godfrey L, Kojima K, Hodgal L, Wunderlich M, Geng H, Marzo I, Harutyunyan KG, Golffman L, North P, Perry J, Ballabio E, Chonghaile TN, Gonzalo O, Qiu Y, Erasmus I, Debose L, O’Brien E, Ma H, Zhou P, Jacamo R, Park E, Coombs KR, Zhang N, Thomas DA, O’Brien S, Kantarjian HM, Leversen JD, Kornblau SM, Andreeff M, Mäschien C, Müller P, Konopleva M. MLL-rearranged acute lymphoblastic leukaemias activate BCL-2 through H3K79 methylation and are sensitive to the BCL-2-specific antagonist ABT-199. Cell Reports 2015; 13(12): 2715–2727 [PubMed: 26711339]

48. Scherr M, Elder A, Battmer K, Barzan D, Bomken S, Ricke-Hoch M, Schröder A, Venturini L, Blair HJ, Vormoor J, Ottmann O, Ganser A, Pich A, Hilfiker-Kleiner D, Heidenreich O, Eder M. Differential expression of miR-17~92 identifies BCL2 as a therapeutic target in BCR-
ABL-positive B-lineage acute lymphoblastic leukemia. Leukemia 2014; 28(3): 554–565 [PubMed: 24280866]

49. Leonard JT, Rowley JS, Eide CA, Traer E, Haynes-Lattin B, Loriaux M, Spurgeon SE, Druker BJ, Tyner JW, Chang BH. Targeting BCL-2 and ABL/LYN in Philadelphia chromosome-positive acute lymphoblastic leukemia. Sci Transl Med 2016; 8(354): 354ra114

50. Fischer U, Forster M, Rinaldi A, Rischt S, Sungalee S, Warnatz HJ, Bornhauser B, Gombert M, Kratsch C, Stütz AM, Sultan M, Tchinda J, Worth CJ, Amstislavskiy V, Badarinarayan N, Baruchel A, Bartram T, Basso G, Canpolat C, Cariò G, Cavé H, Dakaj D, Delorenzi M, Dobay MP, Eckert C, Ellingshaus E, Eugster S, Fris mantas V, Gasparini S, Haas OA, Heidenreich O, Hemmrich-Steinak G, Hezaveh K, Höll J, Hornhardt S, Husemann P, Kacchoo P, Kranz CP, Te Kromm J, Marovca B, Niggl R, McHardy AC, Moorman AV, Panzer-Grünmayer R, Petersen BS, Raeder M, Ralser M, Rosenstiel P, Schäfer M, Schütte M, Stade B, Thiele R, von der Weid N, Vora A, Zaihova M, Zhang L, Zichter T, Zimmermann M, Lehrach H, Bourquin JP, Franke A, Korbel JO, Stanulla M, Yaspo ML. Genomics and drug profiling of fatal TCF3-HLF-positive acute lymphoblastic leukemia identifies recurrent mutational patterns and therapeutic options. Nat Genet 2015; 47(9): 1020–1029 [PubMed: 26214592]

51. Gu Z, Churchman M, Roberts K, Li Y, Liu Y, Harvey RC, McCastlain K, Reshni SC, Payne- Turner D, Iacobucci I, Shao Y, Chen IM, Valentine M, Pei D, Mungall KL, Mungall AJ, Ma Y, Moore R, Marra M, Stonerock E, Gastier-Foster JM, Devidas M, Dai Y, Wood B, Borowitz M, Larsen EE, Maloney K, Mattano LA Jr, Angiolillo A, Salzer WL, Burke M, Gianni F, Spinelli O, Pardina J, Minden MD, Moorman AV, Patel B, Fielding AK, Rowe JM, Luger SM, Bhatia R, Aldoss I, Forman SJ, Kohlschmidt J, Mrózek K, Marucci G, Bloomfield CD, Stock W, Konstantin K, Monge Elia M, Niggli F, McHardy AC, Moorman AV, Panzer-Grünmayer R, Petersen BS, Raeder M, Ralser M, Rosenstiel P, Schäfer D, Schrappe M, Schriepi S, Schütte M, Stade B, Thiele R, von der Weid N, Vora A, Zaihova M, Zhang L, Zichter T, Zimmermann M, Lehrach H, Bourquin JP, Franke A, Korbel JO, Stanulla M, Yaspo ML. Genomics and drug profiling of fatal TCF3-HLF-positive acute lymphoblastic leukemia identifies recurrent mutational patterns and therapeutic options. Nat Genet 2015; 47(9): 1020–1029 [PubMed: 26214592]

52. Yasuda T, Suzaki S, Kawaizawa M, Hayakawa F, Kojima S, Ueno T, Momot K, Ito S, Kishioka S, Kunita A, Doi K, Sakurai T, Kyoji T, Kondo E, Fujimaki K, Ueda Y, Aoyama Y, Ohtake S, Takita J, Sai E, Taniwaki M, Kurokawa M, Morishita S, Fukayama M, Kiyoi H, Miyazaki Y, Naot T, Mano H. Recurrent DUX4 fusions in B cell acute lymphoblastic leukemia of adolescents and young adults. Nat Genet 2016; 48(5): 569–574 [PubMed: 27019113]

53. Suzuki K, Okuno Y, Kawashima N, Muramatsu H, Okuno T, Wang X, Kataoka S, Sekiya Y, Hamada M, Murakami N, Kojima D, Narita K, Narita A, Sakaguchi H, Sakaguchi K, Yoshida N, Nishio N, Hama A, Takahashi Y, Kudo K, Kato K, Kojima S. MEF2D-BCL9 fusion gene is associated with high-risk acute B-cell precursor lymphoblastic leukemia in adolescents. J Clin Oncol 2016; 34(28): 3451–3459 [PubMed: 27507882]

54. Li JF, Dai YT, Lilljebjörn H, Shen SH, Cui BW, Bai L, Liu YF, Qian MX, Kubota Y, Kiyoi H, Matsumura I, Miyazaki Y, Olsson L, Tan AM, Ariffin H, Chen J, Takita J, Yasuda T, Han H, Johansson B, Yang J, Yeoh AE, Hayakawa F, Ren Z, Pui CH, Fioreto T, Chen JN, Huang JY. Transcriptional landscape of B cell precursor acute lymphoblastic leukemia based on an international study of 1,223 cases. Proc Natl Acad Sci USA 2018; 115(50): E11711–E11720 [PubMed: 30487223]

55. Alexander TB, Gu Z, Iacobucci I, Dickerson K, Choi JK, Xu B, Payne-Turner D, Yoshiihara H, Loh ML, Horan J, Buldini B, Basso G, Elitzur S, de Haas V, Zwaan CM, Yeoh A, Reinhardt D, Tomizawa D, Kiyoi H, Matsunaga M, Lammens T, De Moorlose B, Catchpoole D, Horii H, Moorman A, Moore AS, Hrusak O, Meshinchi S, Orgel E, Devidas M, Borowitz M, Wood B, Heerema NA, Carrol A, Yang YL, Smith MA, Davidse TN, Hermida LC, Gesuwan P, Marra MA, Ma Y, Mungall AJ, Moore RA, Jones SM, Valentine M, Janke LJ, Rubnitz JE, Pui CH, Ding L, Liu Y, Zhang J, Nichols KE, Downgar JR, Cao X, Shi L, Pounds S, Newman S, Pei D, Guiraud Avril JM, Gerhard DS, Hunger SP, Inaba H, Mullighan CG. The genetic basis and cell of origin of mixed phenotype acute leukemia. Nature 2018; 562(7727): 373–379 [PubMed: 30209392]

56. Hrusak O, de Haas V, Stanicokova J, Vakmanova B, Janotova I, Meistrikova E, Capek V, Trka J, Zaliqova M, Luks A, Bleckmann K, Möricke A, Irving J, Konatkowska B, Alexander TB, Inaba H, Schmiegelow K, Stokley S, Zemanova Z, Moorman AV, Rossi JG, Felice MS, Dalla-Pozza L, Morales J, Dvorjak M, Buldini B, Basso G, Campbell M, Cabrera ME, Marinov N, Blizurt S, Izraelski S, Loria D, Feuerstein T, Koelenova A, Svec P, Kreminsko O, Rabin KR, Polychronopoulou S, da Costa E, Marquart HV, Kattamis A, Ratei R, Reinhardt D, Choi JK, Schrappe M, Story
J. International cooperative study identifies treatment strategy in childhood ambiguous lineage leukemia. Blood 2018; 132(3): 264–276 [PubMed: 29720486]

57. Harrison CJ, Moorman AV, Schwab C, Carroll AJ, Raetz EA, Devidas M, Strehl S, Nebral K, Harbott J, Teigler-Schlegel A, Zimmerman M, Dastuge N, Baruchel A, Soulier J, Auclerc MF, Attarbaschi A, Mann G, Stark B, Cazzaniga G, Chilton L, Vandenbergh P, Forestier E, Haltrich I, Raimondi SC, Parihar M, Bourquin JP, Tchinda J, Haferlach C, Vora A, Hunger SP, Heerema NA, Haas OA, Ponte di Legno International Workshop in Childhood Acute Lymphoblastic Leukemia. An international study of intrachromosomal amplification of chromosome 21 (iAMP21): cytogenetic characterization and outcome. Leukemia 2014; 28(5): 1015–1021 [PubMed: 24166298]

58. Rafei H, Kantarjian HM, Jabbour EJ. Targeted therapy paves the way for the cure of acute lymphoblastic leukaemia. Br J Haematol 2020; 188(2): 207–223 [PubMed: 31566728]

59. Assi R, Kantarjian H, Short NJ, Daver N, Takahashi K, Garcia-Manero G, DiNardo C, Burger J, Cortes J, Jain N, Wierda W, Chamoun S, Konopleva M, Jabbour E. Safety and efficacy of blinatumomab in combination with a tyrosine kinase inhibitor for the treatment of relapsed Philadelphia chromosome-positive acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk 2017; 17(12): 897–901 [PubMed: 28927784]

60. von Stackelberg A, Locatelli F, Zugmaier G, Handgretinger R, Trippett TM, Rizzi C, Bader P, O’Brien MM, Brethon B, Bhojwani D, Schlegel PG, Borkhardt A, Rheingold SR, Cooper TM, Zwaan CM, Barnette P, Messina C, Michel G, DuBois SG, Hu K, Zhu M, Whillock JA, Gore L. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol 2016; 34(36): 4381–4389 [PubMed: 27998223]

61. Martinelli G, Boissel N, Chevalier P, Ottmann O, Gökbüget N, Topp MS, Fielding AK, Rambaldi A, Ritchie EK, Papayannidis C, Sterling LR, Benjamin J, Stein A. Complete hematologic and molecular response in adult patients with relapsed/refractory Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: results from a phase II, single-arm, multicenter study. J Clin Oncol 2017; 35(16): 1795–1802 [PubMed: 28355115]

62. Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W, Gökbüget N, O’Brien S, Wang K, Wang T, Paccagnella ML, Sleight B, Vandendries E, Advani AS. Inotuzumabozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med 2016; 375(8): 740–753 [PubMed: 27292104]

63. Bhojwani D, Stoppo R, Shah NN, Rodriguez V, Yuan C, Stetler-Stevenson M, O’Brien MM, McNeer JL, Quereshi A, Cabannes A, Schlegel P, Rossig C, Dalla-Pozza L, August K, Alexander S, Bourquin JP, Zwaan M, Raetz EA, Loh ML, Rheingold SR. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. Leukemia 2019; 33(4): 884–892 [PubMed: 30267011]

64. Jabbour E, Sasaki K, Ravandi F, Huang X, Short NJ, Khouri M, Kebrinaei P, Burger J, Khoury J, Jorgensen J, Jain N, Konopleva M, Garcia-Manero G, Kadia T, Cortes J, Jacob J, Montalbano K, Garris R, O’Brien S, Kantarjian HM. Chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD, with or without blinatumomab, is highly effective in patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in first salvage. Cancer 2018; 124(20): 4044–4055 [PubMed: 30307611]

65. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, Bader P, Verneris MR, Stefanski HE, Myers GD, Qayed Y, De Moerloose B, Hiramatsu H, Schlis K, Davis KL, Martin PL, Nemecck ER, Yanik GA, Peters C, Baruchel A, Boissel N, Mechinaud F, Balduzzi A, Krueger J, June CH, Levine BL, Wood P, Taran T, Leung M, Mueller KT, Zhang Y, Sen K, Lebwohl D, Pulipher MA, Grupp SA. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018; 378 (5): 439–448 [PubMed: 29385370]

66. Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, Teacheey DT, Chen A, Hauck B, Wright JF, Milone MC, Levine BL, June CH. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med 2013; 368(16): 1509–1518 [PubMed: 23527958]

67. Chen X, Wang Y, Ruan M, Li J, Zhong M, Li Z, Liu F, Wang S, Chen Y, Liu L, Yang J, Zhu X, Wang J, Pui CH. Treatment of testicular relapse of B-cell acute lymphoblastic leukemia with
CD19-specific chimeric antigen receptor T cells. Clin Lymphoma Myeloma Leuk 2020; 20(6): 366–370 [PubMed: 32205078]

68. Fry TJ, Shah NN, Orentas RJ, Stetler-Stevenson M, Yuan CM, Ramakrishna S, Wolters P, Martin S, Delbrook C, Yates B, Shalabi H, Fountaine TJ, Shern JF, Majzner RG, Stronck Ef, Sabatino M, Feng Y, Dimitrov DS, Zhang L, Nguyen S, Qin H, Dropulic B, Lee DW, Mackall CL. CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. Nat Med 2018; 24(1): 20–28 [PubMed: 30581986]

69. Qin H, Ramakrishna S, Nguyen S, Fountaine TJ, Ponduri A, Stetler-Stevenson M, Yuan CM, Haso W, Shern JF, Shah NN, Fry TJ. Preclinical development of bivalent chimeric antigen receptors targeting both CD19 and CD22. Mol Ther Oncolytics 2018; 11: 127–137 [PubMed: 28539325]

70. Gomes-Silva D, Srinivasan M, Sharma S, Lee CM, Wagner DL, Davis TH, Rounce RH, Bao G, Brenner MK, Mamonkin M. CD7edited T cells expressing a CD7-specific CAR for the therapy of T-cell malignancies. Blood 2017; 130(3): 285–296 [PubMed: 29593621]

71. Fountaine TJ, Vinanica N, Kamiya T, Shimasaki N, Coustan-Smith E, Campana D. Blockade of CD7 expression in T cells for effective chimeric antigen receptor targeting of T-cell malignancies. Blood Adv 2017; 1(25): 2291–2304 [PubMed: 30760212]

72. Cooper ML, Choi J, Rister K, Ritchev JK, Devenport JM, Eckardt K, Rettig MP, Wang B, Eissenberg LG, Gobadi A, Gehrs LN, Prior JL, Achilefu S, Miller CA, Froncek IC, O’Neal J, Gao F, Weinstock DM, Gutierrez A, Fulton RS, DiPersio JF. An “off-the-shelf” fratricide-resistant CAR-T for the treatment of T-cell acute lymphoblastic leukemia. Blood 2019; 133(21): 2348–2360 [PubMed: 30794321]

73. Png YT, Vinanice N, Kamiya T, Shimasaki N, Coustan-Smith E, Campana D. modulation of CD7 expression in T cells for effective chimeric antigen receptor targeting of T-cell malignancies. Blood Adv 2017; 1(25): 2291–2304 [PubMed: 30760212]

74. Rasaiyaah J, Georgiadis C, Preece R, Mock U, Qasim W. TCRαβ/CD3 disruption enables CD3-specific antileukemic T cell immunotherapy. JCI Insight 2018; 3(13): 99442 [PubMed: 29997304]

75. Dunsmore KP, Winter S, Devidas M, Wood BL, Esiashvili N, Eisenberg N, Biegel N, Hayashi RJ, Gistler-Foster JM, Carroll AJ, Heerema NA, Asselin B, Rabin KR, Zweidler-Mckay P, Rael EA, Loh ML, Winick NJ, Carroll WL, Hunger S, Nikko Biegel, Hayashi RJ, Gistler-Foster JM, Carroll AJ, Heerema NA, Asselin B, Rabin KR, Zweidler-Mckay P, Rael EA, Loh ML, Winick NJ, Carroll WL, Hunger S, COG AALL0434: a randomized trial testing nelarabine in newly diagnosed T-cell malignancy. J Clin Oncol 2018; 36(supp 15): 10500

76. Bride KL, Vincent TL, Im SY, Aplenc R, Barrett DM, Carroll WL, Carson R, Dai Y, Devidas M, Dunsmore KP, Fuller T, Glisovic-Aplenc T, Horton TM, Hunger SP, Loh ML, Maude SL, Rael EA, Winter SS, Grupp SA, Hermiston ML, Wood BL, Teachey DT. Preclinical efficacy of daratumumab in T-cell acute lymphoblastic leukemia. Blood 2018; 131(9): 995–999 [PubMed: 29305553]

77. Souers AJ, Leverson JD, Boghaert ER, Ackler SL, Catron ND, Chen J, Dayton BD, Ding H, Enschede SH, Fairbrother WJ, Huang DC, Hymowitz SG, Jin S, Khaw SL, Kovar PJ, Lam LT, Lee J, Mabeeck HL, Marsh KC, Mason KD, Mitten MJ, Nimmer PM, Oleksijew A, Park CH, Park CM, Phillips DC, Roberts AW, Sampath D, Seymour JF, Smith ML, Sullivan GM, Tahir SK, Tse C, Wendt MD, Xiao Y, Xue JC, Zhang H, Humercickhouse RA, Rosenberg SH, Elmore SW. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med 2013; 19(2): 202–208 [PubMed: 23291630]

Front Med. Author manuscript; available in PMC 2022 November 17.
Fig. 1.
Kaplan–Meier and Kalbfleisch and Prentice analyses of outcomes in 598 children with acute lymphoblastic leukemia. The 5-year and 10-year results are shown on the curves.
### Table 1

| Study group | Years of study | No. of patients | Age range (year) | T cell ALL (%) | 5-year cumulative rate of any relapse (%) | 5-year EFS (%) | 5-year survival (%) | Data source |
|-------------|----------------|-----------------|------------------|----------------|------------------------------------------|---------------|---------------------|-------------|
| AIEOP-BFM 2000 | 2000–2006 | 4839 | 1–17 | 13.2 | 13.2 | 81.4±0.6 | 91.9±0.4 | Möricke et al. (2016) [1] |
| CoALL-07-03 | 2003–2010 | 743 | 1–18 | 12.9 | NA | 83±0.3 | NA | Escherich et al. (2013) [2] |
| COG | 2000–2005 | 7153 | 0–22 | 7 | 7.2 | NA | 90.4±0.5 | Hunger et al. (2012) [3] |
| DCOG-10 | 2004–2011 | 778 | 1–18 | 14.2 | 8.3 | 87.0±1.2 | 91.9±1.0 | Pieters et al. (2016) [4] |
| DFCI 05-001 | 2005–2010 | 697 | 1–18 | 0 | 9.0 | 86±3 | 92±2 | Vrooman et al. (2016) [5] |
| EORTC 58951 | 1998–2008 | 1947 | 1–18 | 15.2 | 14.7 | 82.6±0.9 | 89.7±0.7 | Domenech et al. (2014) [6] |
| MRC UKALL 2003 | 2003–2011 | 3126 | 1–25 | 12 | 8.8 | 87.3±1.4 | 91.6±1.2 | Vora et al. (2014) [7] |
| NOPHO-2008 | 2008–2014 | 1022 | 1–9 | 9.1 | 13 | 89±1 | 94±1 | Toft et al. (2018) [8] |
| NOPHO-2008 | 2008–2014 | 266 | 10–17 | 25.2 | 7.0 | 80±3 | 87±2 | Toft et al. (2018) [8] |
| SJCRH 16 | 2000–2017 | 598 | 0–18 | 17.4 | 6.6 | 88.2±3.3 | 94.1±2.4 | Jeha et al. (2019) [9] |
| TPOG | 1999–2010 | 152 | 0–18 | 7.2 | NA | 84.2±3.0 | 90.2±2.4 | Liu et al. (2014) [10] |

Abbreviations: ALL, acute lymphoblastic leukemia; AIEOP, Associazione Italiana di Ematologia Pediatrica Group; BFM, Berlin-Frankfurt-Münster; CoALL, Cooperative ALL Study Group; COG, Children’s Oncology Group; DCOG, Dutch Children’s Oncology Group; DFCI, Dana-Farber Cancer Institute consortium; EFS, event-free survival; EORTC–CLG, European Organisation for Research and Treatment of Cancer–Children Leukemia Group; MRC UKALL, Medical Research Council UK acute lymphoblastic leukemia; NA, not available; NOPHO, Nordic Society of Pediatric Hematology and Oncology; SJCRH, St. Jude Children’s Research Hospital; TPOG, Taiwan Pediatric Oncology Group.

* T-ALL patients not included.
Table 2

Clinical implications and potential therapeutic implications of selected subtypes of ALL

| Subtype                        | Risk group | Therapeutic approach                                                                 |
|-------------------------------|------------|---------------------------------------------------------------------------------------|
| ETV6-RUNX1                    | Low        | Reduced dose intensity if MRD <10^{-4} during early induction or <10^{-5} MRD at the end of induction |
| High-hyperdiploid             | Low        | Reduced dose intensity if MRD <10^{-4} during early induction or <10^{-5} MRD at the end of induction |
| DUX4-rearranged               | Low        | Standard dose intensity, MRD-adapted                                                  |
| ETV6-RUNXI-like               | Standard   | Standard dose intensity, MRD-adapted                                                  |
| TCF3-PBX1                     | Standard   | Standard dose intensity, MRD-adapted, high-dose methotrexate                           |
| PAX5 P80R                     | Intermediate | Standard dose intensity, MRD-adapted                                                |
| PAXalt                        | Intermediate | Standard dose intensity, MRD-adapted                                                |
| ZNF384-rearranged             | Intermediate | Standard dose intensity, MRD-adapted                                                |
| Philadelphia chromosome-positive | High       | ABL tyrosine kinase inhibitors, retinoids, Bcl-2 inhibitors, FAK inhibitors             |
| Philadelphia chromosome-like  | Variable   | Second or third generation ABL tyrosine kinase inhibitors, JAK inhibitors, Bcl-2 inhibitors |
| Hypodiploid                   | High       | Intensive dose intensity, MRD-adapted, Bcl-2 inhibitors                                |
| KMT2A-rearranged              | High       | DOTL1, Menin inhibitors, Bcl-2 inhibitors                                              |
| TCF-HLF                       | High       | Intensive dose intensity, Bcl-2 inhibitors                                              |
| MEF2D-rearranged              | High       | Histone deacetylase inhibitors, bortezomib                                             |
| Early T cell precursor        | High       | Intensive dose intensity, Bcl-2 inhibitors                                              |