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Review Article

Advances in biology of acute lymphoblastic leukemia (ALL) and therapeutic implications

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Abstract: Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer and also occurs in adults. Although the outcomes of multi-agent chemotherapy regimens have greatly improved, high toxicity and relapses in many patients necessitate the development of novel therapeutic approaches. Advances in molecular profiling and cytogenetics have identified a broad range of genetic abnormalities, including gene mutations, chromosome translocations and aneuploidy, which has provided a more comprehensive understanding of the biology and pathogenesis of ALL. This understanding has also led to new targeted therapeutic approaches, including the use of selective small molecule inhibitors, nucleic acid-based therapies and immune-based therapies mediated by specific monoclonal antibodies and cellular immunotherapy, which are poised to revolutionize the treatment of various ALL subtypes. The main focus of this review is to highlight the latest advances in ALL biology, including the identification of prognostic factors and putative therapeutic targets. We also review the current status of, and ongoing progress in, the development of targeted therapies for ALL.

Keywords: Acute lymphoblastic leukemia, leukemia, cytogenetics, molecular subtypes, targeted therapy, immunotherapy

Introduction

Acute lymphoblastic leukemia (ALL) is a malignancy of hematopoietic stem cells that originates from B- and T-lineage lymphoid precursors and is driven by a spectrum of genetic aberrations including mutations, chromosome translocations and aneuploidy in genes involved in the development of lymphoid cells and regulation of cell cycle progression [1]. ALL is the most common childhood cancer (**Figure 1**) with 5-year survival rates of about 90% in children [2-4], and 75-85% in adolescents and young adults. The outcomes in older adults are inferior, with overall survival rates of 35-55% in middle age adults and under 30% in those over age 60 [5-8].

The standard front-line therapeutic approach for treatment of pediatric and adult ALL patients consists of multiagent chemotherapy regimens, followed by hematopoietic stem cell transplantation (HSCT) in high-risk groups [5, 9-12] Although there have been major advances in the treatment of ALL that has resulted in improved overall survival (OS), significant drawbacks of conventional therapies persist, including severe toxicities and the development of chemoresistance leading to relapse. Accordingly the development of novel therapeutic strategies is of utmost importance to improve treatment outcomes [2, 13-15]. This requires a thorough understanding of the biology of this heterogeneous group of diseases.

Both B-ALL and T-ALL subtypes harbor distinct groups of chromosomal rearrangements and sequence mutations affecting lymphoid development, tumor suppression, cytokine receptors, and kinase and other signaling pathways [16] (**Table 1**). Differential gene expression patterns in various ALL subtypes have been identified by a number of techniques, including polymerase chain reaction (PCR), genome-wide sequencing, single nucleotide polymorphism (SNP) array analysis and microarrays. These have provided valuable insights into the biology and pathogenesis of ALL, permitting differentia-

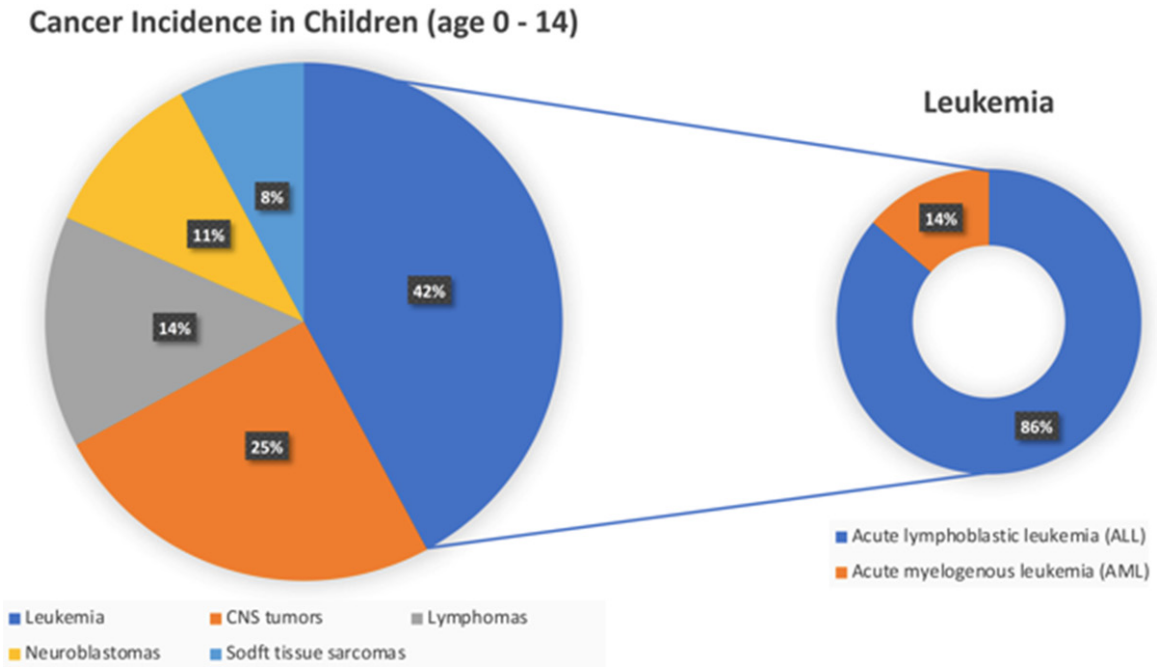

Figure 1. Percent of childhood cancer cases (2006-2013). Adopted from "Canadian Cancer Society-Childhood leukemia statistics" and "Childhood cancer incidence and mortality in Canada" by Lawrence Ellison and Teresa Janz (released in September 2015) [243].

tion into prognostic subgroups, and have highlighted potential therapeutic strategies [17] (**Table 1**).

In this review, advances in the understanding of ALL biology will be discussed. We will then summarize recent studies evaluating molecular and immune-based targeted therapies, and discuss potential novel therapeutic strategies based on our understanding of disease biology.

Genetic subsets of B-cell lymphoblastic leukemia/lymphoma (B-ALL)

BCR-ABL1$^+$ *ALL*

The t(9;22)(q34;q11) translocation, associated with the Philadelphia (Ph) chromosome, is the most common cytogenetic abnormality in adult ALL. The frequency increases with age, occurring in 2-5% of pediatric ALL cases, and 20% of young adults and 30-40% of older adult patients [18, 19]. The Ph chromosome encodes the *BCR-ABL1* fusion oncogenic protein with constitutively active tyrosine kinase activity. The major breakpoint, which creates a 210-kDa protein, is detected in 24-50% of adult Ph$^+$ ALL [20, 21], but is rare in childhood Ph$^+$ ALL [22]. The minor breakpoint, which encodes a 190-kDa protein, is more prevalent and can be identified in 50-77% of adult Ph$^+$ ALL [18, 21] and more than 90% of pediatric cases [23].

Upregulation of *BCR-ABL1* fusion gene leads to activation of multiple signaling pathways such as MAPK, Ras, NF-kB, c-Myc, PI-3 kinase, and JAK-STAT [24]. It also promotes proliferation of lymphoblasts by the alteration of pro- and anti-apoptotic proteins [13]. One of the main genetic alterations in *BCR-ABL1* positive patients is the mutations and deletions in *IKZF1* gene, encoding for the transcription factor Ikaros which is associated with the unfavorable outcomes and poor prognosis in both Ph$^+$ and Ph$^-$ ALL [17, 25, 26]. One study on 83 Ph$^+$ patients demonstrated that 10% lacked *IKZF1* due to chromosome 7 monosomy. Moreover, 63% of patients had a 7p12 deletion of *IKZF1* with different patterns. The most frequent deletions were the loss of exons 4 to 7, detected in 37% of patients, and the loss of exons 2 to 7, detected in 20%. This type of abnormality led to shorter disease-free survival (DFS) compared to patients with *IKZF1* wild type (10 vs. 32 months, P=0.02) [27]. In addition, the time of cumulative incidence of relapse (CIR) was significantly shorter in patients with *IKZF1* deletions versus patients

Table 1. Genetic aberrations and targeting agents associated with different ALL subtypes

ALL subtype	Genetic Aberrations	Targeting Agents	References
BCR-ABL$^+$ ALL	t(9,22)(q34,q11) translocation resulting in BCR-ABL1 fusion protein	Tyrosine kinase inhibitors	[18-20]
	MAPK, Ras, NF-Kβ, C-Myc-PI3K-JAK-STAT pathways, Src family kinases	JAK inhibitors, Proteasome inhibitors	[24]
	Mutations and deletions of *IKZF1* gene	-	[17, 25, 26, 101, 102]
Ph-like B-ALL	Mutations and deletions of *IKZF1, PAX5, EBF1, TCF3, VPREB1* genes	-	[9, 39]
	Overexpression of *CRLF2,* Translocations of *CRLF2* such as P2RY8-CRLF2 and IGH-CRLF2 rearrangements	JAK inhibitors	[25, 40-44] [31, 50]
	EPOR rearrangements, *EPOR* translocations involving 4 partner genes (*IGH, IGK, LAIR1, THADA*)	JAK inhibitors	[25, 40-44]
	Point mutations of *JAK* genes (*JAK1* (V617F), *JAK2* (R683G), *JAK3*)	JAK inhibitors	[15, 40-42, 44-48]
	Rare deletions of *SH2B3*	-	[25]
	Mutations of *IL7R*	-	[25]
	Activation of numerous signaling pathways including PI3K/AKT/mTOR, JAK-STAT, BCL2	JAK inhibitors, mTOR inhibitors	[31, 49-52]
	ABL class fusion genes including translocations of *ABL1, ABL2, PDGFRB, CSF1R*	Tyrosine kinase inhibitors	[15, 25, 28, 31, 35, 52, 53]
	Rearrangements including *ETV6-JAK2, BCR-JAK2, EBF1-PDGFRB, ETV6-NTRK3*	JAK inhibitors, Tyrosine kinase inhibitors	[15, 35, 36, 54-57]
	Translocations involving *FGFR1, TYK2, IL2RB, BLNK, DGKH, LYN, PTK2B, FLT3*, and *RAS* subfamily genes	-	[15, 35, 36, 54-57]
Low hypodiploid ALL	*TP53* mutations	-	[28, 61]
	RB1 alterations	-	[28, 61]
	IKZF2 alterations	-	[28, 61]
Near haploid ALL	*IKZF3* alterations	-	[9, 61, 62]
	Mutations in Ras signalling pathways and PI3K	mTOR inhibitors	[9, 61, 62]
B-ALL with intrachromosomal amplification of chromosome 21 (iAMP21)	Amplification of a portion of chromosome 21	-	[11, 63, 64]
B-ALL with DUX4 and ERG deregulation	Deregulation of DUX4 and ERG	-	[16, 65-68]
B-ALL cases with hyperdiploidy	Overexpression of *SH3BP5* gene	-	[17, 71]
	Disruptions in *CREBBP* gene	-	[72]
Other abnormalities in B-ALL subtypes	MLL rearrangements specially *MLL-AF4* fusion gene	BCL-2 inhibitors	[23, 59]
	TEL-AML1 fusion gene	-	[17, 73, 75]
	E2A-PBX1 fusion gene	-	[23, 76]
	Epigenetic alterations	HDAC inhibitors, DNMT inhibitors	[5, 77, 82]
T-ALL	TCR rearrangements with fusion partners including *TAL2, LYL1, OLIG2, LMO1, LMO2, NKX2-1, NKX2-2, NKX2-5, HOXA*, *MYC*, and *MYB*	-	[16, 87]
	Overexpression of *HOX11, HOX11L2,* and *SCL* genes	-	[23, 84]
	Deletion of *SIL-SCL* gene	-	[84]

	In-frame infusion genes such as *PICALM-MLLT10*, *MLL* gene rearrangements, *SET-NUP214* fusion, *EML1-ABL1, ETV6-ABL1* and *NUP214-ABL1*	JAK inhibitors, BCL-2 inhibitors	[26]
	Sequence mutations in genes such as *NOTCH1*, *FBW7*, *PTPN2*, *MYB*, *NRAS, KRAS*, *PTEN*, *JAK1, JAK3, IL7R*, *STAT5B*, *BCL11B, LEF1, WT1*, *ZEB2*, *SUZ12, PHF6, EZH2, TET2, H3F3A*, *KDM6A CNOT3, RPL5*, *RPL10*	JAK inhibitors	[88, 89]
ETP ALL	Overexpression of *CEBPA, CEBPB, CEBPD,* miR-221, miR-222 and miR-223	JAK inhibitors and chromatin modifying agents	[26, 95-99]
	Mutations in genes including *NRAS, KRAS, IL7R, JAK1, JAK3, NF1, PTPN11*, and *SH2B3*, *FLT3, DNMT3A, IDH1, IDH2, ETV6*, *RUNX1, IKZF1, GATA3*, *EP300, EZH2, SUZ12, EED*, *SETD2*	JAK inhibitors and chromatin modifying agents	[98]

without this aberration (10.1 vs. 56.1 months, respectively; P=0.001) [27].

BCR-ABL positive ALL has been associated with an adverse prognosis and is virtually incurable with chemotherapy alone. The advent of *BCR-ABL1*-directed tyrosine kinase inhibitors (TKIs) has significantly improved the response rates and overall survival rates, particularly when used in combination with chemotherapy, although relapse remains a problem [28, 29].

BCR-ABL1-like (Ph-like) B-ALL

This high-risk subtype of ALL was first detected by Mullighan and colleagues from the Children's Oncology Group (COG) and St. Jude Children's Research Hospital, (SJCRH) and den Boer and colleagues from the Netherlands in 2009. This subtype is characterized by a gene expression pattern similar to that of the *BCR-ABL1* positive ALL cases [17, 30, 31], but without *BCR-ABL1* expression. This so-called Ph-like ALL is more prevalent in adolescents and young adults with B-ALL, comprising about 15% of pediatric B-ALL patients age 12-18 and 20-25% of young adult B-ALL cases [15, 32-35]. It has been associated with an adverse response to induction chemotherapy, a higher frequency of persistent minimal residual disease (MRD) and poor survival [25, 32, 36]. It is the most frequently occurring pediatric and young adult ALL subtype associated with an unfavorable prognosis, with a 5-year disease free survival of about 60% [17, 32].

Different types of genomic alterations have been identified in Ph-like ALL, which are involved in the activation of kinase and cytokine receptor signaling. In addition, more than 80% of Ph-like ALL cases have deletions and/or mutations in genes involved in B-cell development including *IKZF1* (the most frequent aberration), paired box 5 *(PAX5), EBF1*, transcription factor 3 (*TCF3*) and *VPREB1* which encodes the immunoglobulin iota chain [9, 37].

Translocations of *CRLF2* such as *P2Ry8-CRLF2* fusion (detectable by RT-PCR) or *IGH-CRLF2* rearrangements (detectable by FISH), or translocations resulting in truncation and activation of the erythropoietin receptor (*EPOR*) involving four partner genes (*IGH, IGK, LAIR1* and *THADA*), are the common genomic characteristics of Ph-like ALL [38-42]. It has been observed that *EPOR* rearrangements, overexpression of *CRLF2* (detectable by flow cytometry), translocations and point mutations involved in activating JAK proteins, rare deletions of *SH2B3* (encodes the *JAK2*-negative regulator *LNK*) and activation mutations of *IL7R* result in the constitutive activation of JAK-STAT signaling, which explain the resemblance of kinase activity profiles to those of Ph^+ ALL [25]. B-ALL children with Down syndrome (30-50% of cases) are more likely to have CRLF2 translocations along with point mutations in *JAK* genes (*JAK1* (V617F), *JAK2* (R683G), and *JAK3*) [15, 38-40, 42-46]. Upregulation of the thymocyte stromal lymphopoietin receptor (TSLPR) encoded by *CRLF2* gene can be detected by flow cytometry in leukemic cells. This receptor, which is induced by the cytokine *TSLP*, is involved in the activation of numerous signaling pathways, including PI3K/AKT/mTOR and JAK/STAT, that are associated with aberrant proliferation and survival of ALL blasts. Therapeutic approaches targeting PI3K/mTOR, JAK-STAT, and BCL2 signaling pathways have been effective in preclinical models. With the development of *JAK* inhibitors, *JAK* mutations can be considered as potential targets for treatment of this subgroup of ALL patients [31, 47-50].

Another Ph-like-associated genetic aberration involves ABL-class fusion genes, including translocations of *ABL1* (with partners other than *BCR*), *ABL2, PDGFRB* and *CSF1R* (encoding the macrophage colony-stimulating factor receptor) which have been observed in cases with translocations in tyrosine kinases genes. These types of abnormalities have been detected in about 3-5% of childhood ALL patients and 2-3% of adult ALL patients [31, 32, 50]. Preclinical studies suggest that TKIs, including imatinib and dasatinib, may represent effective treatment options for the Ph-like ALL patients with ABL-class fusions [28, 31, 32, 50]. In addition, cases with *ETV6-JAK2* and *BCR-JAK2*-rearrangements are considered as Ph-like variants. It has also been suggested that TKI therapy could be very effective for patients with *EBF1-PDGFRB* translocations [15, 25, 28, 31, 32, 50, 51].

Other rearrangements involving kinase genes such as *ETV6-NTRK3* fusion, *FGFR1, TYK2, IL2RB, BLNK, DGKH, LYN, PTK2B, FLT3* and *RAS* subfamily genes are identified in Ph-like ALL cases [15, 32, 33, 52-55]. Patients with

tyrosine receptor kinase (TRK) fusions are sensitive to TRK inhibitors [56] and ponatinib, which is a kinase inhibitor of *FGFR1* can be considered for cases with *FGFR1* fusion [31].

MLL rearrangements

The t(4;11)(q21;q23) translocation, resulting in the *MLL-AF4* fusion gene, is the most frequently occurring aberration in infants with ALL. This abnormality is also detected in 3-7% of adult ALL cases and confers a poor prognosis [19, 57]. Other *MLL* gene rearrangements can be seen, including *MLL-AF10* in t(10;11), *MLL-AF9* in t(9;11) and *MLL-ENL* in t(11;19). The *MLL* gene, also called *KMT2A*, codes for a histone methyltransferase that regulates gene transcription. Gene expression profiling has identified distinct *MLL*-associated gene signatures in ALL [58].

Hypodiploid B-ALL

This group, characterized by having less than 44 chromosomes, composes 2-3% of ALL patients, and is associated with poor outcomes [59]. It has different subtypes with distinct genetic alterations: Low hypodiploid ALL, with 32 to 39 chromosomes, is associated with several abnormalities, including *TP53* mutations (in 91% of patients), *RB1* (41% of cases) and *IKZF2* alterations (53% of cases). Another subset is the near-haploid ALL with 24 to 31 chromosomes, associated with aberrations such as *IKZF3* alterations (13% of patients) and mutations involved in Ras signaling pathway activation (71% of cases). In pediatric hypodiploid ALL cases, aberrations detected by next-generation sequencing (NGS) include RAS signaling (*NRAS, KRAS, FLT3* and *NF1*), receptor tyrosine kinases (70% of near haploid cases), *IKZF2* and *TP53* mutation% of low hypodiploid cases) [26, 60].

As Ras and PI3K signaling pathways are activated in both near haploid and low-hypodiploid subtypes, these pathways can be considered as potential targets in the treatment of hypodiploid ALL [9, 60, 61].

B-ALL with intrachromosomal amplification of chromosome 21 (iAMP21)

The amplification of a portion of chromosome 21, which can be recognized by FISH using the *RUNX1* gene probe, is the main characteristic of this subtype of ALL. The result of metaphase FISH reveals ≥5 or ≥3 extra copies of genes on a single anomalous chromosome 21. This subtype rarely occurs in adults, but accounts for about 2% of childhood ALL with a higher incidence rate in older children, and patients typically have low WBC counts and a poor prognosis. Patients with this abnormality have been categorized as a standard-risk group; however, studies have revealed a shorter event-free survival (EFS) and overall survival upon treatment based on the standard-risk protocols [11, 62, 63]. More intensified chemotherapy regimens appear to improve the poor prognosis of this entity [64].

B-ALL with DUX4 and ERG deregulation

This recently identified subgroup of B-ALL accounts for about 7% patients. It is characterized by deregulation of the double homeobox 4 gene (*DUX4*) and the *ETS* transcription factor gene (*ERG*). In this subtype, the expression of a truncated isoform of *DUX4* has been identified in the B-cell lineage as a result of *DUX4* rearrangement, while *DUX4* cannot be expressed in normal B cells. This isoform has the ability to bind to the *ERG* intron 6, leading to the deregulation of *ERG* and expression of a noncanonical first exon and transcript, *ERGalt*. This results in the inhibition of the transcriptional activity of wild-type *ERG* and plays an important role in the early initiation of leukemogenesis [16, 64-67]. In general, *DUX4/ERG* deregulated ALL is associated with a good response; however, the presence of other genetic aberrations, including *IKZF1* deletions along with *DUX4/ERG* deregulation, is associated with an unfavorable outcome [16, 68, 69].

Other molecular aberrations in B-ALL

Hyperdiploidy occurs in about 25% of childhood ALL and has a favorable prognosis. These cases have been associated with an approximately ten-fold over-expression of the *SH3BP5* gene, which encodes *SH3*-binding protein 5 located on chromosome 3p24. This protein may be involved in transferring signals from Bruton's tyrosine kinase (BTK) receptor, suggesting this receptor or its downstream signaling pathways may constitute potential therapeutic targets [17, 70]. Disruptions in *CREBBP* gene have also been identified in relapsed hyperdiploid cases [71].

The t(12;21)(p13;q22) translocation, resulting in the *TEL-AML1* (*ETV6-RUNX1*) fusion gene,

accounts for 20-25% of childhood B-ALL. The erythropoietin receptor, which is found in myeloid lineage progenitor cells, can be expressed ~7-fold higher in *ETV6-RUNX1*-positive cases. The upregulation of this gene implies that either *ETV6-RUNX1*-positive cases can express myeloid associated markers, or this gene might have non-erythropoietin related functions [17, 72-74].

Translocation (1;19)(q23;p13.3), occurring in adult B-ALL subtype, generates a chimeric *E2A-PBX1* gene, is seen in ~5% of cases, and has been associated with poor outcome in some studies [19, 75].

About 80% of ALL cases have epigenetic alterations, such as promoter hypermethylation of tumor-suppressor genes, leading to inactivation of tumor-suppressor genes or hypomethylation of oncogenes. Evaluation of epigenetic changes by the use of methylation-specific PCR in ALL is of the utmost importance because different steps involved in this process can be potential targets for many current chemotherapeutic agents including DNA methyltransferase inhibitors [5, 76-81].

Genetic alterations in T-cell acute lymphoblastic leukemia/lymphoma (T-ALL)

T-ALL, comprising 10-15% of ALL cases, has been associated with a number of genetic lesions [61, 82]. The most common T-cell receptor (*TCR*) breakpoint is at 14q11.2, which are the alpha and delta T-cell receptor loci [*TRA* and *TRD*]. In adult T-ALL, *HOX11* gene overexpression resulting from t(10;14)(q24;q11.2) is the most frequent TCR rearrangement [19, 83]. However, in childhood T-ALL, t(1;14)(p32;q11.2) leading to *SCL* (also called *TAL1* or *TCL5*) overexpression (identified in about 3% of cases) and the *SIL-SCL* deletion (chromosome 1 deletion juxtaposing *SCL* and *SIL* genes, which is recognized in 6-26% of cases) are the most common aberrations [83]. Moreover, upregulation of *HOX11L2*, resulting from a cryptic t(5;14)(q35;q32) translocation, is detected in 20-30% of pediatric T-ALL [84, 85]. The *TCR* gene can also be rearranged to other fusion partners such as *TAL2, LYL1, OLIG2, LMO1, LMO2, NKX2-1, NKX2-2, NKX2-5, HOXA* genes, *MYC*, and *MYB* [16, 86]. In addition, in-frame fusion genes encoding oncogenic proteins such as *PICALM-MLLT10*, *MLL* gene rearrangements, *SET-NUP214* fusion, *EML1-ABL1, ETV6-ABL1* and *NUP214-ABL1* fusion formed on episomes, can be caused by chromosomal rearrangements [26].

Common sequence mutations in T-ALL detected by re-sequencing and NGS consist of those in translocation-associated Notch homolog 1 (*NOTCH1*) (detectable in >60% of cases), *FBW7* (detectable in >20% of cases), *PTPN2*, and *MYB*, genes involved in the RAS/PI3K/AKT (*NRAS, KRAS*, and *PTEN*) and JAK-STAT (*JAK1, JAK3, IL7R*, and *STAT5B*) pathways, in transcription regulators (*BCL11B, LEF1, WT1*, and *ZEB2*), in epigenetic regulators (*SUZ12, PHF6, EZH2, TET2, H3F3A*, and *KDM6A*) and in genes associated with the maturation of mRNA and activity of ribosomes (*CNOT3, RPL5*, and *RPL10*) [87, 88]. Cases with mutations in *NOTCH1,* a gene expressing a transmembrane receptor involved in T-cell development, and *FBW7* genes are considered as low-risk patients, while patients who lack these mutations or have mutations involving *RAS/PTEN* are defined as high-risk cases [89-91]. Moreover, *JAK1* mutations are associated with poor prognosis in T-ALL [92, 93].

Early T-precursor (ETP) ALL has recently been identified as a distinct subtype. This heterogeneous subtype shows limited early T-cell differentiation phenotype and has some myeloid and hematopoietic stem cell associated genetic and immunophenotypic features. This subset overexpresses myeloid transcription factors such as *CEBPA, CEBPB, CEBPD* and a group of micro-RNAs, including miR-221, miR-222 and miR-223 [26, 94-98].

Studies of ETP ALL blasts have revealed the presence of mutations in several cellular pathways including Ras, kinase and cytokine receptor signaling genes (*NRAS, KRAS, IL7R, JAK1, JAK3, NF1, PTPN11*, and *SH2B3*), myeloid-associated genes (*FLT3, DNMT3A, IDH1, IDH2* and *ETV6*), genes involved in lymphoid and hematopoietic development (*RUNX1, IKZF1, GATA3*, and *EP300*) and epigenetic regulators with loss-of-function mutations (*EZH2, SUZ12, EED*, and *SETD2*). In this subtype, common gene mutations in typical T-ALL such as mutations in *NOTCH1* (detectable in >60% of T-ALL cases) or *CDKN1/2* are rarely observed [97]. In general, this subgroup has an unfavorable

response to standard therapy; however, current risk adapted therapy may improve the therapeutic outcome [99, 100]. As JAK-STAT and PRC2 pathways are active in ETP-ALL, *JAK* inhibitors and chromatin-modifying agents may be potentially beneficial as therapeutic options [101].

Targeted therapeutic approaches

Small molecule inhibitors

BCR-ABL1-directed TKIs: This class of agents has revolutionized the treatment of BCR-ABL$^+$ B-ALL. When used as single agents combined with corticosteroids, imatinib or dasatinib can produce complete responses in virtually 100% of cases, but usually leads to the rapid emergence of resistant clones, most commonly due to point mutations within the *BCR-ABL* kinase domain, resulting in relapse [28, 29]. Other mechanisms of resistance include increased drug efflux and recruitment of alternative active cell signaling pathways and kinases including *Src*-family kinases leading to cell proliferation and inhibition of apoptosis [102, 103].

These agents have also resulted in significant improvement in treatment outcomes when used in combination with conventional chemotherapy [5, 11, 13]. Imatinib mesylate combined with chemotherapy dramatically increased the 3-year EFS rate from 35% to 80% in pediatric Ph$^+$ ALL compared with chemotherapy alone [104]. The COG AALL0031 study, using the combination of imatinib and intensive chemotherapy, reported equivalent or better 5-year DFS (70%) compared to those who received allogenic HSCT from related or unrelated donors (65% and 59%, respectively) [105]. Children with refractory Ph$^+$ B-ALL demonstrated remissions following treatment with imatinib and dasatinib in combination with chemotherapy [106, 107]. Dasatinib and nilotinib, which are more potent and have activity in some imatinib-resistant clones, have produced remissions in some cases that have relapsed on imatinib therapy [5, 108, 109].

A number of studies have evaluated the use of imatinib, dasatinib and nilotinib, in combination with chemotherapy in adults with Ph$^+$ B-ALL [110-112], which was recently reviewed [113]. Although results are superior to previous studies with chemotherapy alone, relapse due to the emergence of resistant clones remains a problem. The use of dasatinib has been associated with a high frequency of relapse with resistant T315I mutations [112]. More recently, the addition of ponatinib, which is active against resistant T315I clones, to chemotherapy has produced encouraging 3-year EFS in adults with Ph$^+$ ALL [114, 115], and a number of further studies with this agent are either in progress or are being planned.

In Ph-like ALL patients with ABL-class fusions, adding imatinib or dasatinib to combination chemotherapy regimens has resulted in the induction of remissions and clearance of minimal residual disease (MRD) in isolated cases [116-119]. Furthermore, dasatinib was effective in a pediatric Ph-like ALL case with persistent post-transplant MRD [120]. A Phase II clinical trial by MDACC (NCT02420717) is evaluating the use of either ruxolitinib or dasatinib, based on molecular profiling, as initial monotherapy, followed by the addition of Hyper-CVAD chemotherapy [31, 121]. A COG AALL1131 trial (NCT02883049) is currently evaluating the efficacy of dasatinib in Ph-like ALL patients with ABL-class mutations.

PI3K/mTOR inhibitors: Several small molecule inhibitors have been developed to efficiently target different aberrantly activated signaling pathways [9, 13, 14]. One of the constitutive activated signaling pathways in B- and T-ALL is the PI3K/Akt/mTOR pathway which can promote drug resistance, cell proliferation and metabolism. Mammalian target of rapamycin (*mTOR*) which is a downstream target of Akt, functions as a serine/threonine kinase and comprises a core component of two protein complexes: mTORC1 and mTORC2 [2, 9]. mTOR kinase activity can be inhibited by small molecules such as everolimus, temsirolimus, and sirolimus [2, 9]. Studies reported that everolimus induced apoptosis in B-ALL cell lines and reduced enzyme phosphorylation in Akt and mTOR signaling [122-124]. In addition, a Phase I/II trial in relapsed childhood ALL treated with everolimus in combination with hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) reported a CR rate of 25% [125]. Temsirolimus is being evaluated in combination with intensive re-induction therapy through a phase I COG study ADVL1114 in relapsed ALL cases (NCT014-

03415), and also in combination with etoposide, cyclophosphamide, and dexamethasone for children with refractory ALL (NCT01614197). The efficacy of sirolimus plus corticosteroids is under investigation in a Phase I trial in relapsed ALL (NCT00874562).

Dactolisib (BEZ235) is the first dual PI3K/mTOR inhibitor whose efficacy alone and in combination was investigated in clinical trials for hematological malignancies [126-129]. A preclinical study evaluated the effect of BEZ235 on the resistance mechanisms to glucocorticoids which is mediated by constitutive activation of the PI3K/mTOR signaling pathway in T-ALL. The findings demonstrated that BEZ235 enhanced the cytotoxic activity of dexamethasone in various T-ALL cell lines and xenograft models through inhibition of *AKT1* leading to upregulation of pro-apoptotic protein BIM and downregulation of anti-apoptotic protein MCL-1 in an AKT-inactivation independent manner. This study suggested that BEZ235 could be a potential therapeutic option, capable of increasing dexamethasone-induced apoptosis and reversing glucocorticoid resistance in children with T-ALL [130].

BTK inhibitors: BTK, which is a member of the BCR signaling pathway and is involved in the B cell development, can be irreversibly inhibited by ibrutinib. It was reported that ibrutinib could significantly reduce cell proliferation in mouse xenograft models and BCR-positive human ALL cell lines [131-134]. A Phase II trial is assessing ibrutinib efficacy in combination with blinatumomab for adults with relapsed B-ALL (NCT02997761).

JAK/STAT inhibitors: In Ph-like ALL with JAK/STAT pathway alterations, including *CRLF2* rearrangements, JAK mutations, *JAK2* fusions and *EPOR* rearrangements, using ruxolitinib as a selective *JAK* inhibitor, *USP9X* inhibitors, and givinostat as a histone deacetylase inhibitor may constitute potential therapeutic strategies [31, 48, 135-138]. Currently, two clinical trials, COG AALL1521 Phase II trial (NCT02723994) and a subset of SJCRH Total XVII, are evaluating the efficacy of adding ruxolitinib to multi-agent chemotherapy in Ph-like patients with JAK pathway lesions. Moreover, ruxolitinib in combination with chemotherapy is also being investigated by the MD Anderson Cancer Center (MDACC) trial (NCT02420717) in adult and adolescent Ph-like patients with JAK pathway lesions. In this trial, patients receive 3 weeks of ruxolitinib monotherapy followed by multi-agent chemotherapy for patients with an incomplete response. A combination of ruxolitinib, dasatinib and dexamethasone is being assessed in a Phase I trial (NCT02494882) in older patients with newly diagnosed Ph^+ ALL. A recent preclinical study has suggested that targeting STAT5 directly may have therapeutic potential in both $BCR\text{-}ABL^+$ and BCR-ABL-like B-ALL [242].

MEK inhibitors: MAPK/ERK pathway deregulation has been observed in hematologic malignancies as well. 40% of children with relapsed ALL and 6% of Ph-like ALL patients contain mutations in *KRAS* and *NRAS* genes and MAPK signaling pathway [2, 13, 31, 32, 139]. Selumetinib, which is an inhibitor of mitogen-activated protein kinase (*MEK*), has been effective in *RAS* mutated ALL cell line models [2, 139]. Moreover, the cytotoxic effect of concomitant inhibition of MEK and PI3K/AKT pathways was revealed in T-ALL cells [140]. Pimasertib and trametinib are other inhibitors of *MEK1/2*; however, their effects have not been clinically evaluated in ALL [13]. A preclinical study investigated the efficacy of trametinib alone and in combination with BCL-2 inhibitors, ABT-199 and ABT-263, in different B-ALL cell lines and primary B-ALL patient cells. The results demonstrated that trametinib alone could modestly affect the cell viability; however, a combination of *MEK* and *BCL-2* inhibitors showed a synergistic effect and significantly suppressed proliferation and induced apoptosis in B-ALL cells through a MEK/ERK signaling-dependent mechanism mediated by the pro-apoptotic factor *BIM* [6].

FLT3 inhibitors: While mutations of FMS-like tyrosine kinase 3 (*FLT3*) are uncommon in ALL, *FLT3* is highly expressed and often mutated in ALL with MLL rearrangement and in childhood hyperdiploid ALL [141, 142]. Midostaurin, quizartinib, and lestaurtinib are kinase inhibitors with anti-*FLT3* activity [13]. The Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) study (NCT01411267) has evaluated quizartinib in relapsed pediatric ALL. Lestaurtinib is also being explored in infants and young children by a laboratory biomarker study (NCT01150669) and a Phase III trial (NCT00557193), respectively.

PARP inhibitors: Veliparib is an inhibitor of poly (ADP-ribose) polymerase (*PARP*), a protein involved in DNA repair, genomic stability, and programmed cell death. It was observed that veliparib could inhibit cell proliferation by apoptosis induction in human T-ALL cell line models [13, 143]. Multiple clinical trials are now evaluating veliparib in combination with other inhibitors and chemotherapeutic agents in various ALL subgroups including a Phase I, multi-center trial (NCT01139970) investigating veliparib and temozolomide, another Phase I study (NCT00588991) assessing veliparib and topotecan with or without carboplatin and a Phase I/II trial (NCT01326702) evaluating veliparib, bendamustine, and rituximab combination.

Apoptosis inhibitors: YM155 is a small molecule inhibitor of survivin [144], which is a member of the Inhibitor of Apoptosis Protein (IAP) family involved in the cancer development. It was originally suggested to act as a transcriptional suppressor of survivin, but recent evidence is suggesting a multitude of activities in its mechanism of action [145]. Since survivin overexpression was observed in relapsed childhood ALL, [146] the efficacy of YM155 in combination with dasatinib was evaluated in various subtypes of primary ALL samples and ALL cell lines including Ph^+ ALL. The results revealed significant sensitivity of ALL cells to YM155 treatment. In addition to its action on downregulation of survivin expression, its activation of the DNA damage pathway is leading to apoptosis induction and chemo-sensitivity in ALL cells [147].

The B cell lymphoma-2 (*BCL-2*) proteins are involved in the cell death regulation and can prevent apoptosis through binding to anti-apoptotic proteins. *BCL-2* inhibition by selective inhibitors can induce apoptosis in malignant cells. Navitoclax (ABT-263) is believed to inhibit the binding of BCL-2 protein to apoptotic effectors Bax and Bak proteins [148]. It has been evaluated through preclinical xenograft models of B-ALL, T-ALL and *MLL*-mutated ALL and the results were promising [13, 149]. However, navitoclax could not be evaluated in childhood ALL due to dose-limiting thrombocytopenia. Venetoclax (ABT-199) is also a second generation of *BCL-2* inhibitor which showed promising activity in xenograft models of ALL [149]. One study reported that high level of *BCL-2* expression induced by *MLL/AF4* fusion protein was significantly decreased by venetoclax in *MLL*-rearranged ALL cells and also showed a synergistic effect of venetoclax and standard-induction-type chemotherapeutic agents on both *MLL*-rearranged cell lines and xenograft models [150]. A Phase I study has opened evaluating venetoclax and navitoclax in combination with chemotherapy in children and adults with relapsed B-ALL (NCT03181126).

Moreover, *BCL-2* can be upregulated through the tyrosine kinase 2 (*TYK2*) signaling and its downstream effector phospho-*STAT1*. It has been observed that inhibition of heat shock protein 90 (*HSP90*) by its specific small molecule inhibitor NVP-AUY922 (AUY922) resulted in the blockage of *TYK2* signaling and downregulation of phospho-*STAT1* and *BCL-2* in T-ALL cells. In addition, pro-apoptotic proteins BIM and BAD were upregulated by AUY922 which in combination with *BCL-2* downregulation led to induction of apoptosis in T-ALL cells [151].

Proteasome inhibitors: Another aberration in ALL is the deregulation of nuclear factor kappa-B (*NF-κB*), a transcription factor involved in the expression of oncogenes leading to protecting cells from apoptosis. It was observed that *NF-κB* is constitutively activated in different malignancies; inhibition of the activity of *NF-κB* by proteasome inhibitors including bortezomib, carfilzomib, and ixazomib can induce apoptosis in tumor cells or increase the sensitivity of cells to anti-tumor agents [2, 13, 152].

Bortezomib, which inhibits the 26S proteasome reversibly, has been effective in combination with other chemotherapeutics such as dexamethasone, asparaginase, vincristine, doxorubicin, and cytarabine in pre-clinical studies of ALL [153-156]. Different clinical trials have investigated bortezomib in combination with re-induction chemotherapy in ALL patients. A Phase I/II trial of the TACL recruited children with relapsed ALL, with a response rate of 73% [155]; a Phase II AALL07P1 COG study in relapsed B-ALL (61 cases) and T-ALL (17 cases) patients showed CR rates of 69% and 65%, respectively [157]. A Phase II study (NCT01769209) in adult ALL patients, another Phase II trial (NCT02535806) in childhood ALL patients, and a randomized Phase III COG trial (AALL1231) recruiting newly diagnosed young T-ALL patients or stage II-IV T-ALL cases receiv-

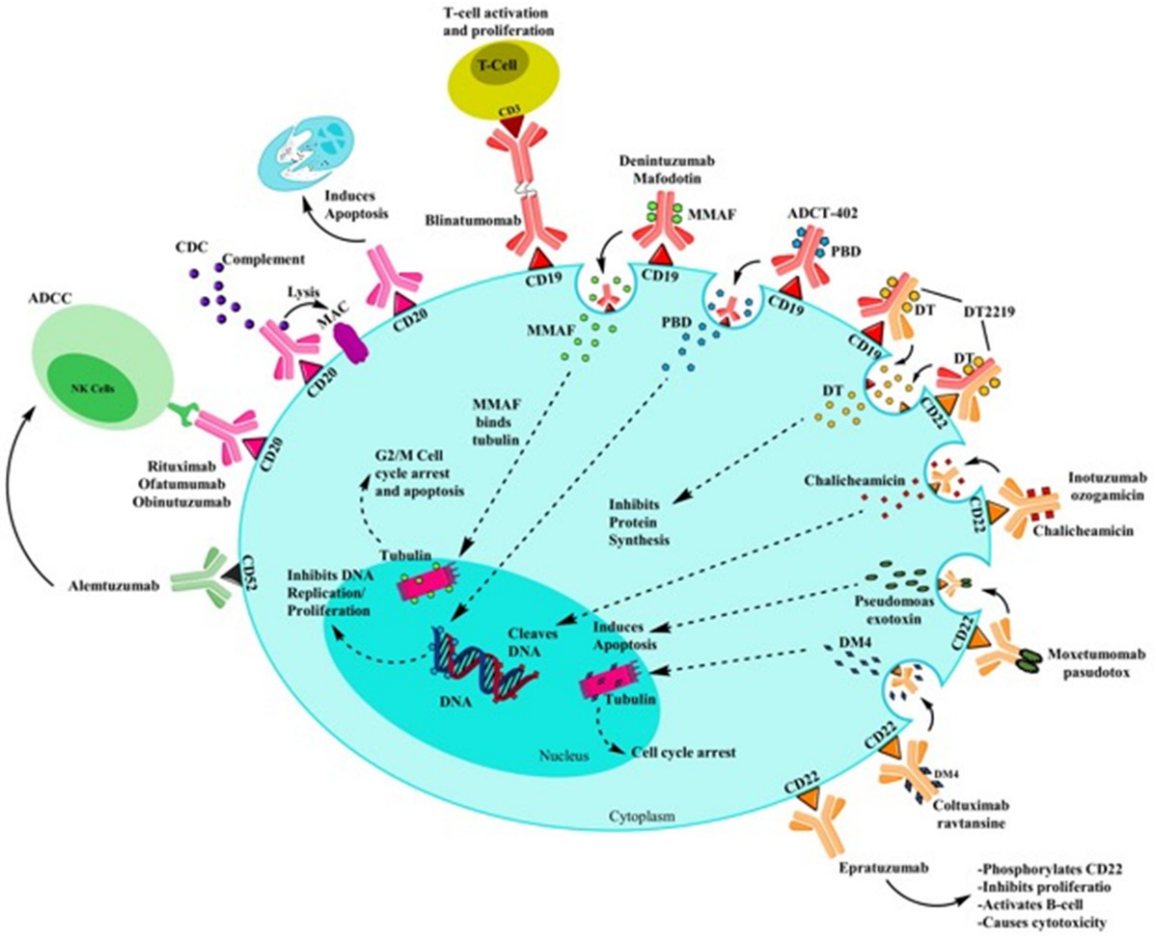

Figure 2. Mechanisms of action for antibody-based targeted therapy. ADCC: antibody-dependent cellular cytotoxicity; NK cells: natural killer cells; CDC: Complement-dependent cytotoxicity; MAC: membrane attack complex; MMAF: monomethyl auristatin F; PBD: Pyrrolobenzodiazepine; DT: diphtheria toxin; DM4: maytansinoid.

ing chemotherapy with or without bortezomib (NCT02112916), are investigating the effectiveness of bortezomib. The efficacy of bortezomib in combination with other inhibitors including HDAC inhibitors which target epigenetic-related abnormalities has been evaluated; however, the results are yet to be published.

Carfilzomib, a more potent proteasome inhibitor with higher specificity [13], was investigated by a Phase I trial (NCT01137747) for AML and ALL cases in 2014 but the outcomes were not published. Moreover, a Phase I study (NCT02293109) is evaluating the optimal tolerable dose of carfilzomib in combination with hyper-CVAD, and another study (NCT02228772) is exploring the tolerability and safety of carfilzomib combined with re-induction chemotherapy in patients with refractory ALL. Ixazomib, another proteasome inhibitor, is under investigation in combination with chemotherapy by a Phase I trial (NCT02228772) for ALL patients.

Inhibitors of epigenetic modifications: Epigenetic abnormalities have been also considered a significant source of transformations in ALL. Deacetylation of lysine residue on histones mediated by histone deacetylase inhibitors (HDACs) is an epigenetic abnormality leading to silencing of the transcription of tumor suppressor genes [152]. Therefore, inhibition of HDACs can stop cell proliferation and induce programmed cell death. Belinostat, vorinostat, and panobinostat are HDAC inhibitors, [13] which have been investigated through several clinical trials in ALL patients. Relapsed ALL patients were treated in a Phase II study (NCT01483690) with a combination of vorinostat, decitabine and chemotherapy; however, high toxicity resulted in the termination of the

study. A Phase I trial (NCT00348985) investigated the effect of the combination of belinostat and bortezomib on adult patients with refractory T-ALL, but the outcomes were not published. The effectiveness of panobinostat in combination with bortezomib, liposomal vincristine and salvage therapy is being evaluated in a Phase II study (NCT02518750) in children and young adults with refractory T-ALL.

DNA methylation of cytosine-phosphate diesterguanine (CpG) islands by DNA methyltransferases (DNMTs) is another epigenetic silencing mechanism resulting in suppression of tumor suppressor genes. Cytosine analogs, including azacitidine and decitabine, are hypomethylating agents which inhibit DNMTs through incorporation into DNA and RNA and induction of apoptosis in abnormal hematopoietic cells. Azacitidine and decitabine with and without HDAC inhibitors demonstrated promising results in relapsed ALL cell line models [158]. Furthermore, patients with refractory AML and ALL were treated in a Phase I TACL trial with azacitidine in combination with chemotherapy and was well-tolerated. However, the high toxicity associated with the combination of decitabine, vorinostat and chemotherapy in children with relapsed ALL caused termination of the pilot TACL study (NCT01483690).

Antibody-based immunotherapy

Recently, several mAbs have been developed to target specific markers mostly expressed on B-cell lymphoblasts including CD20, CD19, CD22 and CD52 (**Figure 2**). In addition, cytotoxic T-cell responses can be activated by new immunotherapeutic approaches [2, 9, 13].

Anti-CD20 mAbs: CD20, which is expressed on the surface of 30-50% of B cell lymphoblasts, can be targeted by rituximab, ofatumumab, and obinutuzumab [13, 159] (**Figure 2**). Rituximab is a chimeric anti-CD20 mAb which was approved in 1997 for non-Hodgkin lymphoma [160]. Binding of rituximab to CD20 removes B cells from circulation through complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity (ADCC), and apoptosis induction (**Figure 2**). It has been observed that rituximab improved the efficacy of induction and consolidation chemotherapy and increased the CR and OS in $CD20^+$ ALL patients [13, 159]. In the GRAALL-2005 study, rituximab was combined with chemotherapy and improved 2-year EFS and 2-year OS (65% vs. 52%; P=0.038 and 74% vs. 63%; P=0.018, respectively) in patients with Ph^-, $CD20^+$ B-ALL [161, 162].

Ofatumumab, which was approved in 2009 for CLL [163], is a humanized type I mAb, and obinutuzumab (GA101) is a glycoengineered humanized type II anti-CD20 mAb [164, 165] (**Figure 2**). Ofatumumab targets the small-loop epitope on CD20 and it has higher complement-dependent cytotoxicity compared to rituximab, while obinutuzumab has lower complement- and antibody-dependent cytotoxicity and little direct cytotoxicity [164, 165]. Ofatumumab is being investigated in a Phase II clinical trial (NCT02419469) in combination with the augmented BFM in B-ALL patients. In another Phase II trial, ofatumumab in combination with hyper-CVAD increased the 3-year continuous CR rate to 78% and the 3-year OS to 68% in newly diagnosed ALL patients [166]. In addition, preclinical studies revealed that the cell death was induced in rituximab-sensitive or rituximab-resistant precursor B-ALL xenografted mice by obinutuzumab [167].

Anti-CD19 mAbs: CD 19, which is highly expressed on the surface of >90% of B-ALL blasts, is the target for blinatumomab and denintuzumab mafodotin [13] (**Figure 2**). Blinatumomab is a bispecific T cell engager (BiTE) antibody, which binds to CD3 on T cells and CD19 on B lymphoblasts, resulting in the release of inflammatory cytokines, proliferation of T cells and $CD19^+$ cell lysis (**Figure 2**). Initial studies in relapsed/refractory pediatric B-ALL patients demonstrated promising results, with 40-60% of patients achieving CR [168]. In 2016, blinatumomab was approved by the US FDA for the treatment of adult patients with relapsed Ph^- ALL based on Phase II data [169]. It has also been shown to be capable of eradicating MRD in ALL [170], and this may improve outcomes post-HSCT [171]. The Phase III TOWER study assessed the efficacy of blinatumomab compared to the standard chemotherapy in adults with relapsed/refractory B-ALL [172]. This trial demonstrated a superior CR rate and improved OS with blinatumomab compared to standard therapy (7.7 vs. 4 months and 39 vs. 19%, respectively). Treatment was more effective in patients with lower tumor burdens. Other trials (NCT02143414, NCT02003-

222 and NCT02807883) are evaluating blinatumomab in different settings, including frontline and maintenance therapy. Side effects associated with blinatumomab, including cytokine release syndrome and neurologic toxicities, necessitate close observation during the early stages of infusion [13].

Denintuzumab mafodotin (SGN-CD19A) which is an antibody drug conjugate (ADC) links a humanized anti-CD19 antibody to the monomethyl auristatin F (MMAF), a drug that induces apoptosis by inhibiting the microtubule assembly and triggering G2/M arrest upon binding to CD19 and internalization [173] (**Figure 2**). Denintuzumab mafodotin was applied for the treatment of relapsed B-ALL patients in a Phase I trial, and 22% and 35% of patients demonstrated CR or PR following the weekly treatment and once in 3 weeks of treatment, respectively [174].

ADCT-402 is also an ADC which links a humanized anti-CD19 antibody to a cytotoxic dimer, pyrrolobenzodiazepine, leading to inhibition of both DNA replication and proliferation of $CD19^+$ blasts (**Figure 2**). ADCT-402 demonstrated significant cytotoxicity in $CD19^+$ cell lines and improved the survival of xenograft models [175]. The efficacy of ADCT-402 is currently under investigation for relapsed B-ALL cases in a Phase I clinical study (NCT02669264).

DT2219 is a bispecific recombinant mAb targeting both CD19 and CD22 and contains the catalytic and translocation domains of diphtheria toxin (DT390) and two sFv subunits recognizing CD19 and CD22. In vitro studies demonstrated favorable results in B cell leukemia models [176, 177] (**Figure 2**). In a Phase I dose escalation study, only one patient out of 25 adolescents and adults with relapsed $CD22^+$, $CD19^+$ B-ALL achieved a partial response [178]. Efficacy of DT2219 is now being evaluated in a Phase II trial in adults and children older than 12 years (NCT02370160).

Anti-CD22 mAbs: CD22 is another specific B cell lineage antigen expressed by 90% of B-ALL lymphoblasts and is a potential target for inotuzumab ozogamicin, moxetumomab pasudotox, coltuximab ravtansine, and epratuzumab [13, 159, 179] (**Figure 2**). Inotuzumab ozogamicin, which is an ADC, includes a humanized anti-CD22 IgG4 mAb and calicheamicin, a cytotoxic agent resulting in DNA breakage following the linkage and internalization of CD22 and anti-CD22 [180, 181] (**Figure 2**). In the Phase III INO-VATE trial (NCT01564784), relapsed/refractory $CD22^+$ ALL patients treated with inotuzumab ozogamicin experienced higher CR rates and superior OS compared to a control group treated with standard chemotherapy (80.7 vs. 29.4%; $P < 0.001$, 7.7 vs. 6.7 months; $P=0.04$) [182]. This agent has also been approved by the FDA and other regulatory bodies. Other ongoing clinical trials are also evaluating inotuzumab ozogamicin in combination with chemotherapy in relapsed ALL patients (NCT01925131), in combination with frontline chemotherapy regimens (NCT03150693, NCT01371630), and in combination with bendamustine, fludarabine +/- rituximab as conditioning therapy with an allogeneic HSCT (NCT01664910).

Moxetumomab pasudotox is a recombinant antibody comprising the variable fragment of an anti-CD22 antibody and part of a Pseudomonas exotoxin which can induce apoptosis upon internalization [183]. This agent is being studied in a Phase I/II study in refractory ALL patients (NCT01891981). Coltuximab ravtansine (SAR3419) is also an ADC which includes an anti-CD22 antibody and maytansinoid (DM4), a cytotoxic agent that induces cell cycle arrest through the inhibition of microtubule assembly and tubulin polymerization following internalization. However, a phase II trial in relapsed ALL did not yield favorable results [183].

Epratuzumab is a humanized anti-CD22 mAb that is internalized upon binding to the third extracellular domain of CD22. It can induce CD22 phosphorylation, inhibition of proliferation, B-cell activation and cytotoxicity (**Figure 2**). The results of a Phase II COG trial showed that combining epratuzumab with standard reinduction chemotherapy could not improve the rates of achieving a second CR in relapsed B-ALL [13, 185]. Epratuzumab is being evaluated in combination with cytarabine and clofarabine in another Phase II trial (NCT00945815) in refractory ALL. Adult with relapsed ALL have shown an overall response rate of 40-52% following treatment with epratuzumab and chemotherapy [186].

Anti-CD52 mAb: Alemtuzumab is a recombinant mAb against CD52, expressed in 36-66% of leukemic blasts, which causes ADCC-mediated lysis of $CD52^+$ cells [13, 159, 187]

(**Figure 2**). However, there are limitations and side effects associated with its use in ALL patients, including lymphopenia resulting in severe and prolonged immunosuppression, and it did not show promising results in several trials [159]. Alemtuzumab is currently being applied in a clinical trial for refractory chronic or acute adult T-cell leukemia in combination with recombinant human IL-15 (NCT02689453).

Anti-PD-1 mAb: Nivolumab, which is a humanized mAb against anti-programmed cell death protein-1 (PD-1), can induce immunosurveillance of malignant cells [13, 188]. The efficacy of this mAb in combination with dasatinib is being assessed in a Phase I study for relapsed Ph^+ ALL patients (NCT02819804). Furthermore, the poor-risk relapsed $CD19^+$ B-ALL patients treated with the combination of blinatumomab and nivolumab with or without ipilimumab, are being evaluated by a Phase I study (NCT02879695).

Cellular immunotherapy

A novel targeted therapeutic approach for B-ALL utilizes chimeric antigen receptor-modified T-cells (CAR T-cells) which are specific for B-cell antigens. In this approach, an antibody is expressed by the patients' own genetically engineered cytotoxic T cells recognizing B-cell antigens. In the CAR structure, an extracellular antigen-recognition domain from a mAb fragment (scFv) is linked to the intracellular signaling domains of the T-cell receptor complex by CARs. This results in the activation of T-cells in a major histocompatibility complex-independent manner yielding a potent cytotoxic response [2, 189]. In the second and third generations of CAR T-cells, one (second) or two (third) costimulatory domains including CD28 or CD27, CD137 (4-1BB), ICOS, and CD134 (OX40) are incorporated to increase the persistence of engineered T cells and achieve higher cytokine production and replicative capacity [190-193]. Preclinical data indicated that CD19-targeted CAR T-cells display enhanced cytotoxicity in vitro and in murine xenograft models [194].

CAR T-cell therapy has yielded remarkable activity in patients with relapsed and refractory B-ALL, with CR rates in the 70-90% range [195-197]. In a Phase I study in 2014, 21 ALL patients (children and young adults) were treated with CD19 CAR T-cells (maximum tolerated dose: 1×10^6 CD19-CAR T-cells/kg), 70% achieving CR [197]. In another report in 2014, 90% (27 out of 30) of childhood and adult patients with relapsed ALL achieved CR with CTL019 cells, and these cells were detectable at least for 6 months in 68% of cases [198]. In Sept. 2017, the FDA approved the first CAR T-cell therapy (Tisagenlecleucel) for relapsed/refractory B-ALL in patient under age 25, and many other CAR T trials in B-ALL are in progress. CAR T-cell therapy is associated with several acute adverse effects including hypotension related to the inflammatory cytokine level in serum, fevers and cytokine release syndrome (CRS), which can develop into macrophage activating syndrome [198, 199]. These effects can be mitigated by tocilizumab, an ani-IL6 monoclonal antibody [200, 201].

The outcome of CAR T therapy is affected by the durability of CAR T-cells in patients. This limitation can be addressed by reinfusion of 'fresh' CAR T-cells [202, 203]. Emergence of CD19 negative B cells is another reason for CAR-T therapy failure. A study by Lacey *et al.* identified a relapsed CD19 negative leukemia originated from a CTL019 treated clone [204]. These CD19 negative B-cells escaped from CAR T therapy by downregulation of surface CD19 target antigen in a cell autonomous manner. Developing CAR T-cells to target additional antigens on the surface of B-cells is a promising approach to prevent the relapse. CAR T-cells targeting CD22 have been explored to treat CD19 negative B-cells in some studies, and the results revealed that CD22 is a promising target in relapsed B-ALL patients pre-treated with CD19 CAR T-cells [205-207]. Innovative strategies to improve the efficacy of CAR T-cell therapy include using combined CD19 and CD22 CAR T-cells, vaccination to increase the CAR T-cells persistence, use of allogeneic T-cells or even cord blood T-cells, induction of apoptosis in CAR T-cells, and sleeping beauty transposon system [208, 209].

RNAi-mediated and related therapy

The development of drug resistance leading to relapse and toxicity due to off-target effects are serious limitations associated with conventional therapeutic strategies [2, 9, 11, 210, 211]. To address these limitations and develop a

more specific approach, RNA interference (RNAi) based therapy is being explored with promising results in pre-clinical settings [212, 213]. The RNAi targets the complementary mRNA for degradation or inhibition of translation and, therefore, can selectively silence the expression of the aberrant proteins involved in uncontrolled cell proliferation. As RNAi functions at a molecular level to downregulate its target mRNA with a high degree of specificity, its activity is minimally affected by point mutations which results in drug resistance [211, 214].

RNAi-mediated therapy can be carried out by delivery of short hairpin RNA (shRNA) encoded by an expression vector (viruses or plasmid DNA for non-viral means), antisense oligonucleotides (ASO; typically 16-20 b.p. single-stranded DNA polynucleotides) or double stranded small interfering RNA (siRNA; typically 19-27 polynucleotides) [211, 215]. However, the latter approaches require an efficient delivery system since polynucleotides are highly unstable in serum due to presence of nucleases, and their anionic nature prevents them from traversing cellular membranes. Among different carrier systems, cationic hydrophobic biomolecules are the most frequently used carries for intracellular delivery of anionic polynucleotides due to safety reasons; unlike viral vectors, they do not integrate into host genome, offering safe delivery of polynucleotides. They can be chemically modified for different purposes [211, 214, 216].

A number of potential targets in B-ALL have been identified for downregulation by RNAi (**Table 2**). These targets can be categorized based on their role in the development of leukemia and include those mediating proliferation, apoptosis, chemo-sensitivity, mediating B-cell differentiation and regulating the mobility of cancer cells [211, 217]. One of the potential targets in ALL is CD22 without exon 12 (CD22ΔE12) which normal B cells lack. Therefore, siRNA mediated silencing of this specific target will not affect the normal B cell function. One study showed that CD22ΔE12 siRNAs delivered by liposome and cationic peptide carriers reduced clonogenicity of B-ALL cells and added to the cytotoxic effects of chemotherapy agents *in vitro*. Furthermore, infusion of this construct inhibited the growth of B-ALL in a mouse xenograft model [216, 217] (**Table 2**).

High expression of certain isoforms of histone deacetylases (HDAC) is also associated with poor outcomes in ALL. One study reported that the chemo-sensitivity of T-cells increased in an ALL model treated by HDAC siRNA [220]. Another study investigated silencing of MAX dimerization protein 3 (MXD3) which is a basic-helix-loop-helix-leucine-zipper transcription factor involved in cellular proliferation [116, 221, 222]. It has been demonstrated that MXD3 functions as an anti-apoptotic protein, and therefore, downregulation of MXD3 may be beneficial for B-ALL [223, 224].

Ab-mediated delivery of polynucleotides, which can specifically target the leukemic cells, is also promising, as it reduces their non-specific delivery into non-leukemic cells. To knockdown *MXD3*, a nanoparticle (NP) formulation of super paramagnetic iron oxide (SPIO) with *MXD3* ASO conjugated to anti-CD22 Ab (αCD22 Ab) was developed to target B-ALL cells. The results revealed significant *in vitro* and downregulation of *MXD3* mRNA, with induction of apoptosis and sensitization to chemotherapeutics; it also demonstrated anti-leukemic activity in B-ALL xenograft mouse models [225] (**Table 2**).

Hsp32, which functions as a survival factor in cancer cells, is another target for RNAi-mediated therapy. The role of Hsp32 was explored in ALL patient and cell line models by Cerny-Reiterer *et al.* [226]. ATL1102 is a second-generation antisense oligonucleotide against human α4 integrin (CD49d/ITGA4) RNA. CD49d is involved in signal transduction, adhesion and proliferation of cells [227, 228] and its silencing by ATL1102 in chemo-resistant human Kasumi-2 B-ALL cells decreased the expression of CD49d protein; however, these results could not be confirmed in mouse xenograft models [229] (**Table 2**).

A recent preclinical study evaluated the therapeutic effect of lipid NP encapsulated *TCF3-PBX1* siRNA *in vitro* on the *TCF3-PBX1*-expressing 697 cells and *in vivo* on a patient-derived xenograft (PDX) model from a *TCF3-PBX1*-positive B-ALL patient [230, 231]. *TCF3-PBX1* was significantly downregulated by the specific siRNA at both mRNA and protein levels. Moreover, an efficient uptake of the NP/siRNA

Table 2. A list molecular targets, delivery systems and cell models applied to investigate nucleic acid-based therapy in ALL

Molecular Targets	Delivery agent	Cell models	References
CD22ΔE12	Liposome (DOTAP/DOPE) and Cationic peptides (PVBLG)	B-ALL xenograft models	[203, 210, 211]
HDAC	Electroporation	Human T-ALL cell line (CCRF-CEM)	[212]
MXD3	Super paramagnetic iron oxide nanoparticles	Jurkat: T-ALL, Reh: B-ALL cells	[217]
CD49d	Nucleofection/Incubation	Chemo-resistant human Kasumi-2 B-ALL cells/Mouse model of B-ALL	[221]
HSP 32	Lipofection	ALL patient cells	[218]
TCF3-PBX1	Lipid nanoparticles	*TCF3-PBX1*-expressing 697 cells/ patient-derived xenograft (PDX) model from a *TCF3-PBX1*-positive B-ALL patient	[222, 223]
RP11-137H2.4	Nucleofection	NALM6 B-ALL cells, Reh prednisolone-resistant B-ALL cells	[224-226, 231]
PIK1	Self-delivery of siRNNs	T-ALL cell line models and patient samples	[229-232]

formulation was observed in difficult-to-transfect patient CML and ALL cells, which confirmed the potency of the siRNA delivery system. *In vivo* studies demonstrated that siRNA-mediated silencing of the *TCF3-PBX1* fusion oncogene improved survival in *TCF3-PBX1* dependent B-ALL PDX mice compared to the control group [230] (median OS 45 days vs. 32 days, P=0.0026) (**Table 2**).

MicroRNAs (miRNA) are endogenous non-coding RNA molecules (typically 19 to 25 nucleotides with partial base pairing) that are involved in regulating the expression of genes as well as other mRNAs [213, 215]. Long non-coding RNAs (lncRNAs) are a new category of non-coding RNAs that are capable of regulating different cellular processes leading to tumorigenesis. Recent studies have reported that some specific lncRNAs are deregulated in pediatric B-ALL and they can be utilized as potential therapeutic targets [215, 232-235]. *RP11-137H2.4* is a lncRNA which plays an important regulatory role in apoptosis, proliferation, and migration of leukemic blasts. It has been observed that silencing the expression of *RP11-137H2.4*, through its specific siRNA, induced apoptosis and inhibited migration in NALM6 B-ALL cells. In addition, transducing Reh prednisolone-resistant B-ALL cells with a shRNA targeting *RP11-137H2.4*, sensitized cells to glucocorticoids by modulating the expression of MAPK cascade genes [232] (**Table 2**).

RNAi prodrugs were recently derived from modified short interfering Ribonucleic Neutrals (siRNNs), which can enter the cells without a delivery system. Upon internalization, cytoplasmic enzymes cleave the siRNNs into regular siRNAs which are capable of inhibiting their target mRNAs [236]. The therapeutic efficacy of RNAi prodrugs against polo-like kinase 1 (*Plk1*), which has a key role in mitosis regulation and its upregulation is associated with unfavorable outcomes [237-240], was evaluated by a preclinical study in pediatric T-ALL cell line models and patient samples. *PIK1* siRNNs significantly inhibited *PIK1* at both mRNA and protein levels and induced apoptosis and G2/M arrest in T-ALL patient cells, with less toxic effect on normal cells [239].

Concluding remarks and future perspectives

Strategies to analyze the molecular genetic and epigenetic aberrations in leukemic cells have resulted in a more comprehensive understanding of the molecular mechanisms leading to chemotherapy drug resistance and adverse outcomes in ALL. The genomic approaches, combined with transcriptional profiling and proteomics, are yielding ever greater insights into ALL pathogenesis and biology, and will result in an expanding repertoire of targeted therapies for clinical evaluation. Ultimately, these emerging technologies should lead to a new era of individualized molecular medicine, resulting in more effective and less toxic regimens [5, 83]. While improved diagnosis and individualized therapy are expected to improve outcomes, it will also further fragment patient populations into sub-populations based on possible 'therapeutic' targets. Libraries of different TKIs, Abs targeting different epitopes, and CAR T-cells with different specificities will all help the physician in the choice of individualized therapies. Molecular therapies relying on nucleic acids (RNAi and similar approaches) will be more convenient to adopt since changing target specificity of nucleic acids can be accomplished relatively easily. This approach will provide an effective way to combat relapsing disease, provided the molecular signature of the emerging population is understood.

Advances in targeted therapeutics have already yielded a series of effective targeted immunotherapies. However, with the exception of *BCR-ABL1*-directed TKIs in Ph^+ ALL, the use of therapeutic approaches to downregulate aberrant signaling and apoptotic pathways in ALL remains investigational. Considerable clinical research will be required to evaluate the potential utility of selective potent small molecule inhibitors targeting other aberrant pathways in ALL. Given the likely emergence of drug resistance against small molecular entities, and the multiplicity and redundancy of such signaling pathways, these agents will likely need to be used in combination with other chemotherapeutic or immunotherapeutic approaches. It will be important to systematically investigate upstream (e.g., JAK) vs. downstream signaling pathways (e.g., STATs) for their relative efficacy. Combinational inhibition of signaling pathways will be useful, but whether interfering with multiple sequential steps in a signaling pathway, or interfering parallel pathways will need to be evaluated for their relative efficacy. RNAi offers another promising avenue of targeted therapy,

potentially avoiding the emergence of drug resistance; however, effective delivery systems will need to be optimized before this approach can be widely applied. Detection of minimal residual disease using flow cytometry, and molecular analysis for identifying mutations and genetic signatures [14, 85], will be necessary to optimally evaluate the response to such therapies [241].

Disclosure of conflict of interest

None.

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References

[1] Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. N Engl J Med 2015; 373: 1541-52.
[2] Santiago R, Vairy S, Sinnett D, Krajinovic M, Bittencourt H. Novel therapy for childhood acute lymphoblastic leukemia. Expert Opin Pharmacother 2017; 18: 1081-99.
[3] Smith M, Seibel N, Altekruse S, Ries L, Melbert D, Reaman G. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 2010; 28: 2625-34.
[4] Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992-2004). Cancer 2008; 112: 416-32.
[5] Faderl S, O'Brien S, Pui CH, Stock W, Wetzler M, Kantarjian HM. Adult acute lymphoblastic leukemia. Cancer 2010; 116: 1165-76.
[6] Korfi K, Smith M, Swan J, Somervaille TC, Dhomen N, Marais R. BIM mediates synergistic killing of B-cell acute lymphoblastic leukemia cells by BCL-2 and MEK inhibitors. Cell Death Dis 2016; 7: e2177.
[7] Gökbuget N, Kneba M, Raff T, Trautmann H, Bartram CR, Hoelzer D. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood 2012; 120: 1868-76.
[8] Ribera JM, Oriol A, Morgades M, Montesinos P, Sarrà J, Feliu E. Treatment of high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in adolescents and adults according to early cytologic response and minimal residual disease after consolidation assessed by flow cytometry: final results of the PETHEMA. J Clin Oncol 2014; 32: 1595-604.
[9] Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer J 2017; 7: e577.
[10] National Comprehensive Cancer Network. Acute lymphoblastic leukemia. Natl Compr Canc Netw 2017; 15: 1535-48.
[11] Kato M, Manabe A. Treatment and biology of pediatric acute lymphoblastic leukemia. Pediatr Int 2018; 60: 4-12.
[12] Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. Pediatr Clin North Am 2015; 62: 61-73.
[13] Man LM, Morris AL, Keng M. New Therapeutic strategies in acute lymphocytic leukemia. Curr Hematol Malig Rep 2017; 12: 197-206.
[14] Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. J Clin Oncol 2011; 29: 532-43.
[15] Reshmi SC, Harvey RC, Roberts KG, Stonerock E, Smith A, Hunger SP. Targetable kinase gene fusions in high-risk B-ALL: a study from the children's oncology group. Blood 2017; 129: 3352-62.
[16] Iacobucci I, Mullighan CG. Genetic basis of acute lymphoblastic leukemia. J Clin Oncol 2017; 35: 975-83.
[17] Den Boer ML, van Slegtenhorst M, De Menezes RX, Cheok MH, Buijs-Gladdines JG, Peters ST, Van Zutven LJ, Beverloo HB, Van der Spek PJ, Escherich G, Horstmann MA, Janka-Schaub GE, Kamps WA, Evans WE, Pieters R. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol 2009; 10: 125-34.
[18] Gleißner B, Gökbuget N, Bartram CR, Janssen B, Rieder H, Thiel E. Leading prognostic relevance of the BCR-ABL translocation in adult acute B-lineage lymphoblastic leukemia: a prospective study of the german multicenter trial group and confirmed polymerase chain reaction analysis. Blood 2002; 99: 1536-43.
[19] Cytogenetic abnormalities in adult acute lymphoblastic leukemia: correlations with hematologic findings outcome. A collaborative study of the group français de cytogénétique hématologique. Blood 1996; 87: 3135-42.
[20] Westbrook CA, Hooberman AL, Spino C, Dodge RK, Larson RA, Bloomfield CD. Clinical significance of the BCR-ABL fusion gene in adult acute lymphoblastic leukemia: a cancer and leukemia group B study (8762). Blood 1992; 80: 2983-90.
[21] Rieder H, Ludwig WD, Gassmann W, Maurer J, Janssen JW, Fonatsch C. Prognostic significance of additional chromosome abnormalities in adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia. Br J Haematol 1996; 95: 678-91.
[22] Chissoe SL, Bodenteich A, Wang YF, Wang YP, Burian D, Roe BA. Sequence and analysis of

the human ABL gene, the BCR gene, and regions involved in the Philadelphia chromosomal translocation. Genomics 1995; 27: 67-82.
[23] Jain N, Roberts KG, Jabbour E, Patel K, Eterovic AK, Konopleva M. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. Blood 2017; 129: 572-81.
[24] Sattler M, Griffin JD. Mechanisms of transformation by the BCR/ABL oncogene. Int J Hematol 2001; 73: 278-91.
[25] Roberts KG, Morin RD, Zhang J, Hirst M, Zhao Y, Richard P. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. Cancer Cell 2013; 22: 153-66.
[26] Chiaretti S, Zini G, Bassan R. Diagnosis and subclassification of acute lymphoblastic leukemia. Mediterr J Hematol Infect Dis 2014; 6: e2014073.
[27] Martinelli G, Iacobucci I, Storlazzi CT, Vignetti M, Paoloni F, Fo R. IKZF1 (Ikaros) deletions in BCR-ABL1-positive acute lymphoblastic leukemia are associated with short disease-free survival and high rate of cumulative incidence of relapse: a GIMEMA AL WP report. J Clin Oncol 2009; 27: 5202-7.
[28] Liu-Dumlao T, Kantarjian H, Thomas DA, O'Brien S, Ravandi F. Philadelphia-positive acute lymphoblastic leukemia: current treatment options. Curr Oncol Rep 2012; 14: 387-94.
[29] Hughes T, Deininger M, Hochhaus A, Branford S, Radich J, Goldman JM. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006; 108: 28-37.
[30] Mullighan CG, Su X, Zhang J, Radtke I, Phillips LA, Miller CB, Ma J, Liu W, Cheng C, Schulman BA, Harvey RC, Chen IM, Clifford RJ, Carroll WL, Reaman G, Bowman WP, Devidas M, Gerhard DS, Yang W, Relling MV, Shurtleff SA, Campana D, Borowitz MJ, Pui CH, Smith M, Hunger SP, Willman CL, Downing JR; Children's Oncology Group. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med 2009; 360: 470-80.
[31] Tasian SK, Loh ML and Hunger SP. Philadelphia chromosome-like acute lymphoblastic leukemia. Blood 2017; 130: 2064-72.
[32] Roberts KG, Li Y, Payne-Turner D, Harvey RC, Yang YL, Mullighan CG. Targetable kinase-activating lesions in ph-like acute lymphoblastic leukemia. N Engl J Med 2014; 371: 1005-15.
[33] Roberts KG, Gu Z, Payne-Turner D, McCastlain K, Harvey RC, Mullighan CG. High frequency and poor outcome of philadelphia chromosome-like acute lymphoblastic leukemia in adults. J Clin Oncol 2016; 35: JCO2016690073.
[34] van der Veer A, Waanders E, Pieters R, Willemse ME, Van Reijmersdal SV, Russell LJ, Harrison CJ, Evans WE, van der Velden VH, Hoogerbrugge PM, Van Leeuwen F, Escherich G, Horstmann MA, Mohammadi Khankahdani L, Rizopoulos D, De Groot-Kruseman HA, Sonneveld E, Kuiper RP, Den Boer ML. Independent prognostic value of BCR-ABL1-like signature and IKZF1 deletion, but not high CRLF2 expression, in children with B-cell precursor ALL. Blood 2013; 122: 2622-9.
[35] Boer JM, Koenders JE, Van Der Holt B, Exalto C, Sanders MA, Rijneveld AW. Expression profiling of adult acute lymphoblastic leukemia identifies a BCR-ABL1-like subgroup characterized by high non-response and relapse rates. Haematologica 2015; 100: e261-4.
[36] Hunger SP, Mullighan CG. Redefining ALL classification: Toward detecting high-risk ALL and implementing precision medicine. Blood 2015; 125: 3977-87.
[37] Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan-Smith E, Downing JR. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature 2007; 446: 758-64.
[38] Mullighan CG, Collins-Underwood JR, Phillips LA, Loudin MG, Liu W, Zhang J, Ma J, Coustan-Smith E, Harvey RC, Willman CL, Mikhail FM, Meyer J, Carroll AJ, Williams RT, Cheng J, Heerema NA, Basso G, Pession A, Pui CH, Raimondi SC, Hunger SP, Downing JR, Carroll WL, Rabin KR. Rearrangement of CRLF2 in B-progenitor- and Down syndrome-associated acute lymphoblastic leukemia. Nat Genet 2009; 41: 1243-6.
[39] Russell LJ, Capasso M, Vater I, Akasaka T, Bernard OA, Harrison CJ. Deregulated expression of cytokine receptor gene, CRLF2, is involved in lymphoid transformation in B-cell precursor acute lymphoblastic leukemia. Blood 2009; 114: 2688-98.
[40] Harvey RC, Mullighan CG, Chen IM, Wharton W, Mikhail FM, Willman CL. Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. Blood 2010; 115: 5312-21.
[41] Yoda A, Yoda Y, Chiaretti S, Bar-Natan M, Mani K, Weinstock DM. Functional screening identifies CRLF2 in precursor B-cell acute lymphoblastic leukemia. Proc Natl Acad Sci U S A 2010; 107: 252-7.
[42] Hertzberg L, Vendramini E, Ganmore I, Cazzaniga G, Schmitz M, Izraeli S. Down syndrome acute lymphoblastic leukemia, a highly heterogeneous disease in which aberrant expression of CRLF2 is associated with mutated JAK2: a

report from the international BFM study group. Blood 2010; 115: 1006-17.
[43] Russell LJ, Jones L, Enshaei A, Tonin S, Ryan SL, Harrison CJ. Characterisation of the genomic landscape of CRLF2-rearranged acute lymphoblastic leukemia. Genes Chromosom Cancer 2017; 56: 363-72.
[44] Bercovich D, Ganmore I, Scott LM, Wainreb G, Birger Y, Izraeli S. Mutations of JAK2 in acute lymphoblastic leukaemias associated with Down's syndrome. Lancet 2008; 372: 1484-92.
[45] Gaikwad A, Rye CL, Devidas M, Heerema NA, Carroll AJ, Rabin KR. Prevalence and clinical correlates of JAK2 mutations in down syndrome acute lymphoblastic leukaemia. Br J Haematol 2009; 144: 930-2.
[46] Kearney L, Gonzalez De Castro D, Yeung J, Procter J, Horsley SW, Eguchi-Ishimae M, Bateman CM, Anderson K, Chaplin T, Young BD, Harrison CJ, Kempski H, So CW, Ford AM, Greaves M. Specific JAK2 mutation (JAK2R683) and multiple gene deletions in down syndrome acute lymphoblastic leukemia. Blood 2009; 113: 646-8.
[47] Scheeren FA, Van Lent AU, Nagasawa M, Weijer K, Spits H, Blom B. Thymic stromal lymphopoietin induces early human B-cell proliferation and differentiation. Eur J Immunol 2010; 40: 955-65.
[48] Maude SL, Tasian SK, Vincent T, Hall JW, Sheen C, Teachey DT. Targeting JAK1/2 and mTOR in murine xenograft models of Ph-like acute lymphoblastic leukemia. Blood 2012; 120: 3510-8.
[49] Waibel M, Solomon VS, Knight DA, Ralli RA, Kim SK, Johnstone RW. Combined targeting of JAK2 and Bcl-2/Bcl-xL to cure mutant JAK2-driven malignancies and overcome acquired resistance to JAK2 inhibitors. Cell Rep 2013; 5: 1047-59.
[50] Roberts KG. The biology of Philadelphia chromosome-like ALL. Best Pract Res Clin Haematol 2017; 30: 212-21.
[51] Iacobucci I, Li Y, Roberts KG, Dobson SM, Kim JC, Mullighan CG. Truncating erythropoietin receptor rearrangements in acute lymphoblastic leukemia. Cancer Cell 2016; 29: 186-200.
[52] Yano M, Imamura T, Asai D, Kiyokawa N, Nakabayashi K, Sato A. Identification of novel kinase fusion transcripts in paediatric B cell precursor acute lymphoblastic leukaemia with IKZF1 deletion. Br J Haematol 2015; 171: 813-7.
[53] Imamura T, Kiyokawa N, Kato M, Imai C, Okamoto Y, Shimada H. Characterization of pediatric Philadelphia-negative B-cell precursor acute lymphoblastic leukemia with kinase fusions in Japan. Blood Cancer J 2016; 6: e419.
[54] Sakamoto K, Imamura T, Kanayama T, Yano M, Asai D, Sato A. Ph-like acute lymphoblastic leukemia with a novel PAX5-KIDINS220 fusion transcript. Genes Chromosom Cancer 2017; 56: 278-84.
[55] Baldazzi C, Iacobucci I, Luatti S, Ottaviani E, Marzocchi G, Paolini S, Stacchini M, Papayannidis C, Gamberini C, Martinelli G, Baccarani M, Testoni N. B-cell acute lymphoblastic leukemia as evolution of a 8p11 myeloproliferative syndrome with t(8;22)(p11;q11) and BCR-FGFR1 fusion gene. Leuk Res 2010; 34: e282-5.
[56] Hyman DM, Laetsch TW, Kummar S, DuBois SG, Farago AF, Drilon AE. The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers. J Clin Oncol 2017; 35: LBA2501-LBA2501.
[57] Wetzler M, Dodge RK, Mrózek K, Carroll AJ, Tantravahi R, Block AW, Pettenati MJ, Le Beau MM, Frankel SR, Stewart CC, Szatrowski TP, Schiffer CA, Larson RA, Bloomfield CD. Prospective karyotype analysis in adult acute lymphoblastic leukemia: the cancer and leukemia group B experience. Blood 1999; 93: 3983-93.
[58] Zangrando A, Dell'Orto MC, Te Kronnie G and Basso G. MLL rearrangements in pediatric acute lymphoblastic and myeloblastic leukemias: MLL specific and lineage specific signatures. BMC Med Genomics 2009; 2: 36.
[59] Moorman AV, Harrison CJ, Buck GA, Richards SM, Secker-Walker LM, Dewald GW. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the medical research council (MRC) UKALLXII/eastern cooperative oncology group (ECOG) 2993 trial. Blood 2007; 109: 3189-97.
[60] Holmfeldt L, Wei L, Diaz-Flores E, Walsh M, Zhang J, Mullighan CG. The genomic landscape of hypodiploid acute lymphoblastic leukemia. Nat Genet 2013; 45: 242-52.
[61] Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classi fi cation of myeloid neoplasms and acute leukemia. Blood 2016; 127: 2391-406.
[62] Harrison CJ, Moorman AV, Schwab C, Carroll AJ, Raetz EA, Haas OA. An international study of intrachromosomal amplification of chromosome 21 (iAMP21): cytogenetic characterization and outcome. Leukemia 2014; 28: 1015-21.
[63] Moorman AV, Robinson H, Schwab C, Richards SM, Hancock J, Harrison CJ. Risk-directed treatment intensification significantly reduces the risk of relapse among children and adolescents with acute lymphoblastic leukemia and intrachromosomal amplification of chromosome 21: a comparison of the MRC ALL97/99 and UKALL2003 trials. J Clin Oncol 2013; 31: 3389-96.

[64] Liu YF, Wang BY, Zhang WN, Huang JY, Li BS, Chen SJ. Genomic profiling of adult and pediatric b-cell acute lymphoblastic leukemia. EBioMedicine 2016; 8: 173-83.
[65] Yasuda T, Tsuzuki S, Kawazu M, Hayakawa F, Kojima S, Mano H. Recurrent DUX4 fusions in B cell acute lymphoblastic leukemia of adolescents and young adults. Nat Genet 2016; 48: 569-74.
[66] Zhang J, McCastlain K, Yoshihara H, Xu B, Chang Y, Mullighan CG. Deregulation of DUX4 and ERG in acute lymphoblastic leukemia. Nat Genet 2016; 48: 1481-9.
[67] Lilljebjörn H, Henningsson R, Hyrenius-Wittsten A, Olsson L, Orsmark-Pietras C, von Palffy S, Askmyr M, Rissler M, Schrappe M, Cario G, Castor A, Pronk 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: 11790.
[68] Harvey RC, Mullighan CG, Wang X, Dobbin KK, Davidson GS, Willman CL. Identification of novel cluster groups in pediatric high-risk B-precursor acute lymphoblastic leukemia with gene expression profiling: correlation with genome-wide DNA copy number alterations, clinical characteristics, and outcome. Blood 2010; 116: 4874-84.
[69] Clappier E, Auclerc MF, Rapion J, Bakkus M, Caye A, Cavé H. An intragenic ERG deletion is a marker of an oncogenic subtype of B-cell precursor acute lymphoblastic leukemia with a favorable outcome despite frequent IKZF1 deletions. Leukemia 2014; 28: 70-7.
[70] Uckun FM, Zheng Y, Cetkovic-Cvrlje M, Vassilev A, Lisowski E, Chen CL. In vivo pharmacokinetic features, toxicity profile, and chemosensitizing activity of α-cyano-β-hydroxy-β-methyl-N-(2,5-dibromophenyl)propenamide (LFM-A13), a novel antileukemic agent targeting Bruton's tyrosine kinase. Clin Cancer Res 2002; 8: 1224-33.
[71] Mühlbacher V, Zenger M, Schnittger S, Weissmann S, Kunze F, Haferlach C. Acute lymphoblastic leukemia with low hypodiploid/near triploid karyotype is a specific clinical entity and exhibits a very high TP53 mutation frequency of 93%. Genes Chromosom Cancer 2014; 53: 524-36.
[72] Ross M, Zhou X. Classification of pediatric acute lymphoblastic leukemia by gene expression profiling. Blood 2003; 102: 2951-9.
[73] Fine BM, Stanulla M, Schrappe M, Ho M, Viehmann S, Boxer LM. Gene expression patterns associated with recurrent chromosomal translocations in acute lymphoblastic leukemia. Blood 2004; 103: 1043-9.
[74] Baruchel A, Cayuela JM, Ballerini P, Landman-Parker J, Cezard V, Sigaux F. The majority of myeloid-antigen-positive (My+) childhood B-cell precursor acute lymphoblastic leukaemias express TEL-AML1 fusion transcripts. Br J Haematol 1997; 99: 101-6.
[75] Khalidi HS, O'Donnell MR, Slovak ML, Arber DA. Adult precursor-B acute lymphoblastic leukemia with translocations involving chromosome band 19p13 is associated with poor prognosis. Cancer Genet Cytogenet 1999; 109: 58-65.
[76] Garcia-Manero G, Yang H, Kuang SQ, O'Brien S, Thomas D, Kantarjian H. Epigenetics of acute lymphocytic leukemia. Semin Hematol 2009; 46: 24-32.
[77] Roman-Gomez J, Jimenez-Velasco A, Barrios M, Prosper F, Heiniger A, Agirre X. Poor prognosis in acute lymphoblastic leukemia may relate to promoter hypermethylation of cancer-related genes. Leuk Lymphoma 2007; 48: 1269-82.
[78] Roman-Gomez J, Agirre X, Jiménez-Velasco A, Arqueros V, Vilas-Zornoza A, Prosper F. Epigenetic regulation of MicroRNAs in acute lymphoblastic leukemia. J Clin Oncol 2009; 27: 1316-22.
[79] Issa JP. DNA methylation as a therapeutic target in cancer. Clin Cancer Res 2007; 13: 1634-7.
[80] Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, Harris NL, Le Beau MM, Hellström-Lindberg E, Tefferi A, Bloomfield CD. The 2008 revision of the WHO classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2008; 114: 937-52.
[81] McGregor S, McNeer J, Gurbuxani S. Beyond the 2008 world health organization classification: the role of the hematopathology laboratory in the diagnosis and management of acute lymphoblastic leukemia. Semin Diagn Pathol 2012; 29: 2-11.
[82] Meijerink JP. Genetic rearrangements in relation to immunophenotype and outcome in T-cell acute lymphoblastic leukaemia. Best Pract Res Clin Haematol 2010; 23: 307-18.
[83] Mrózek K, Heerema NA, Bloomfield CD. Cytogenetics in acute leukemia. Blood Rev 2004; 18: 115-36.
[84] Bernard OA, Busson-LeConiat M, Ballerini P, Mauchauffé M, Della Valle V, Berger R. A new recurrent and specific cryptic translocation, t(5;14)(q35;q32), is associated with expression of the Hox11L2 gene in T acute lymphoblastic leukemia. Leukemia 2001; 15: 1495-504.
[85] Hélias C, Leymaire V, Entz-Werle N, Falkenrodt A, Eyer D, Lessard M. Translocation t(5;14)(q35;q32) in three cases of childhood T cell

acute lymphoblastic leukemia: a new recurring and cryptic abnormality. Leukemia 2002; 16: 7-12.
[86] Ferrando AA, Neuberg DS, Staunton J, Loh ML, Huard C, Look AT. Gene expression signatures define novel oncogenic pathways in T cell acute lymphoblastic leukemia. Cancer Cell 2002; 1: 75-87.
[87] Durinck K, Goossens S, Peirs S, Wallaert A, Van Loocke W, Matthijssens F, Pieters T, Milani G, Lammens T, Rondou P, Van Roy N, De Moerloose B, Benoit Y, Haigh J, Speleman F, Poppe B, Van Vlierberghe P. Novel biological insights in T-cell acute lymphoblastic leukemia. Exp Hematol 2015; 43: 625-39.
[88] Weng AP, Ferrando AA, Lee W, Morris JP, Silverman LB, Aster JC. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science 2004; 306: 269-71.
[89] Park MJ, Taki T, Oda M, Watanabe T, Yumura-Yagi K, Hayashi Y. FBXW7 and NOTCH1 mutations in childhood T cell acute lymphoblastic leukaemia and T cell non-Hodgkin lymphoma. Br J Haematol 2009; 145: 198-206.
[90] Trinquand A, Tanguy-Schmidt A, Ben Abdelali R, Lambert J, Beldjord K, Lengliné E, De Gunzburg N, Payet-Bornet D, Lhermitte L, Mossafa H, Lhéritier V, Bond J, Huguet F, Buzyn A, Leguay T, Cahn JY, Thomas X, Chalandon Y, Delannoy A, Bonmati C, Maury S, Nadel B, Macintyre E, Ifrah N, Dombret H, Asnafi V. Toward a NOTCH1/FBXW7/RAS/PTEN-based oncogenetic risk classification of adult T-Cell acute lymphoblastic leukemia: a group for research in adult acute lymphoblastic leukemia study. J Clin Oncol 2013; 31: 4333-42.
[91] Asnafi V, Buzyn A, Le Noir S, Baleydier F, Simon A, Macintyre E. NOTCH1/FBXW7 mutation identifies a large subgroup with favorable outcome in adult T-cell acute lymphoblastic leukemia (T-ALL): a group for research on adult acute lymphoblastic leukemia (GRAALL) study. Blood 2009; 113: 3918-24.
[92] Flex E, Petrangeli V, Stella L, Chiaretti S, Hornakova T, Tartaglia M. Somatically acquired JAK1 mutations in adult acute lymphoblastic leukemia. J Exp Med 2008; 205: 751-8.
[93] Asnafi V, Le Noir S, Lhermitte L, Gardin C, Legrand F, MacIntyre E. JAK1 mutations are not frequent events in adult T-ALL: a GRAALL study. Br J Haematol 2010; 148: 178-9.
[94] Coustan-Smith E, Mullighan CG, Onciu M, Behm FG, Raimondi SC, Campana D. Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia. Lancet Oncol 2009; 10: 147-56.
[95] Chiaretti S, Messina M, Tavolaro S, Zardo G, Elia L, Foà R. Gene expression profiling identifies a subset of adult T-cell acute lymphoblastic leukemia with myeloid-like gene features and over-expression of miR-223. Haematologica 2010; 95: 1114-21.
[96] Coskun E, Neumann M, Schlee C, Liebertz F, Heesch S, Baldus CD. MicroRNA profiling reveals aberrant microRNA expression in adult ETP-ALL and functional studies implicate a role for miR-222 in acute leukemia. Leuk Res 2013; 37: 647-56.
[97] Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Mullighan CG. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature 2012; 481: 157-63.
[98] Jain N, Lamb AV, O'Brien S, Ravandi F, Konopleva M, Khoury JD. Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype. Blood 2016; 127: 1863-9.
[99] Borowitz MJ, Wood BL, Devidas M, Loh ML, Raetz EA, Larsen E. Prognostic significance of minimal residual disease in high risk B-ALL: a report from children's oncology group study AALL0232. Blood 2015; 126: 964-71.
[100] Patrick K, Wade R, Goulden N, Mitchell C, Moorman AV, Vora A. Outcome for children and young people with early T-cell precursor acute lymphoblastic leukaemia treated on a contemporary protocol, UKALL 2003. Br J Haematol 2014; 166: 421-4.
[101] Maude SL, Dolai S, Delgado-Martin C, Vincent T, Robbins A, Teachey DT. Efficacy of JAK/STAT pathway inhibition in murine xenograft models of early T-cell precursor (ETP) acute lymphoblastic leukemia. Blood 2015; 125: 1759-67.
[102] Hu Y, Liu Y, Pelletier S, Buchdunger E, Warmuth M, Li S. Requirement of Src kinases Lyn, Hck and Fgr for BCR-ABL1-induced B-lymphoblastic leukemia but not chronic myeloid leukemia. Nat Genet 2004; 36: 453-61.
[103] Hu Y, Swerdlow S, Duffy TM, Weinmann R, Lee FY, Li S. Targeting multiple kinase pathways in leukemic progenitors and stem cells is essential for improved treatment of Ph^+ leukemia in mice. Proc Natl Acad Sci 2006; 103: 16870-5.
[104] Schultz KR, Bowman WP, Aledo A, Slayton WB, Sather H, Camitta B. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol 2009; 27: 5175-81.
[105] Schultz KR, Carroll A, Heerema NA, Bowman WP, Aledo A, Camitta B. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: children's oncology group study AALL0031. Leukemia 2014; 28: 1467-71.
[106] Lengline E, Beldjord K, Dombret H, Soulier J, Boissel N, Clappier E. Successful tyrosine kinase inhibitor therapy in a refractory B-cell precursor acute lymphoblastic leukemia with

EBF1-PDGFRB fusion. Haematologica 2013; 98: e146-8.
[107] Crombet O, Lastrapes K, Zieske A, Morales-Arias J. Complete morphologic and molecular remission after introduction of dasatinib in the treatment of a pediatric patient with t-cell acute lymphoblastic leukemia and ABL1 amplification. Pediatr Blood Cancer 2012; 59: 333-4.
[108] Ottmann O, Dombret H, Martinelli G, Simonsson B, Guilhot F, Coutre S. Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. Blood 2007; 110: 2309-15.
[109] Kantarjian H, Giles F, Wunderle L, Bhalla K, O'Brien S, Ottmann OG. Nilotinib in imatinib-resistant CML and philadelphia chromosome-positive ALL. N Engl J Med 2006; 354: 2542-51.
[110] Ravandi F, Jorgensen JL, Thomas DA, O'Brien S, Garris R, Kantarjian HM. Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy. Blood 2013; 122: 1214-21.
[111] Rousselot P, Coudé MM, Gokbuget N, Passerini CG, Hayette S, Ottmann OG. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. Blood 2016; 128: 774-82.
[112] Kim DY, Joo YD, Lim SN, Kim SD, Lee JH, Jeong SH. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood 2015; 126: 746-56.
[113] Saini L, Brandwein J. New treatment strategies for philadelphia chromosome-positive acute lymphoblastic leukemia. Curr Hematol Malig Rep 2017; 12: 136-42.
[114] Jabbour E, Kantarjian H, Ravandi F, Thomas D, Huang X, O'Brien S. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. Lancet Oncol 2015; 16: 1547-55.
[115] Sasaki K, Jabbour EJ, Ravandi F, Short NJ, Thomas DA, Kantarjian HM. Hyper-CVAD plus ponatinib versus hyper-CVAD plus dasatinib as frontline therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: a propensity score analysis. Cancer 2016; 122: 3650-6.
[116] Yun JS, Rust JM, Ishimaru T, Diaz E. A novel role of the mad family member mad3 in cerebellar granule neuron precursor proliferation. Mol Cell Biol 2007; 27: 8178-89.
[117] Bhojwani D, Pui CH. Relapsed childhood acute lymphoblastic leukaemia. Lancet Oncol 2013; 14: e205-17.
[118] Daver N, O'Brien S. Novel therapeutic strategies in adult acute lymphoblastic leukemia--a focus on emerging monoclonal antibodies. Curr Hematol Malig Rep 2013; 8: 123-31.
[119] Sievers EL, Linenberger M. Mylotarg: antibody-targeted chemotherapy comes of age. Curr Opin Oncol 2001; 13: 522-7.
[120] Kobayashi K, Miyagawa N, Mitsui K, Matsuoka M, Kojima Y, Ohara A. TKI dasatinib monotherapy for a patient with Ph-like ALL bearing AT-F7IP/PDGFRB translocation. Pediatr Blood Cancer 2015; 62: 1058-60.
[121] Wells J, Jain N, Konopleva M. Philadelphia chromosome-like acute lymphoblastic leukemia: progress in a new cancer subtype. Clin Adv Hematol Oncol 2017; 15: 554-61.
[122] Neri LM, Cani A, Martelli AM, Simioni C, Junghanss C, Capitani S. Targeting the PI3K/Akt/mTOR signaling pathway in B-precursor acute lymphoblastic leukemia and its therapeutic potential. Leukemia 2014; 28: 739-48.
[123] Brown VI, Fang J, Alcorn K, Barr R, Kim JM, Grupp SA. Rapamycin is active against B-precursor leukemia in vitro and in vivo, an effect that is modulated by IL-7-mediated signaling. Proc Natl Acad Sci U S A 2003; 100: 15113-8.
[124] Teachey DT, Obzut DA, Cooperman J, Fang J, Carroll M, Grupp SA. The mTOR inhibitor CCI-779 induces apoptosis and inhibits growth in preclinical models of primary adult human ALL. Blood 2006; 107: 1149-55.
[125] Daver N, Boumber Y, Kantarjian H, Ravandi F, Cortes J, Konopleva M. A phase I/II study of the mTOR inhibitor everolimus in combination with hyperCVAD chemotherapy in patients with relapsed/refractory acute lymphoblastic leukemia. Clin Cancer Res 2015; 21: 2704-14.
[126] Wunderle L, Badura S, Lang F, Wolf A, Schleyer E, Serve H, Goekbuget N, Pfeifer H, Bug G, Ottmann OG. Safety and efficacy of BEZ235, a dual PI3-Kinase/mTOR inhibitor, in adult patients with relapsed or refractory acute Leukemia: results of a phase I study. Blood 2013; 122: 2675.
[127] Maira SM, Stauffer F, Brueggen J, Furet P, Schnell C, Fritsch C, Brachmann S, Chène P, De Pover A, Schoemaker K, Fabbro D, Gabriel D, Simonen M, Murphy L, Finan P, Sellers W, García-Echeverría C. Identification and characterization of NVP-BEZ235, a new orally available dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor with potent in vivo antitumor activity. Mol Cancer Ther 2008; 7: 1851-63.
[128] Salkeni MA, Rixe O, Karim NA, Ogara S, Feiler M, Moorthy G, Mercer CA, Thomas H, Desai PB, Fathallah H, Kozma S, Thomas G, Morris JC. BEZ235 in combination with everoli-

mus for advanced solid malignancies: preliminary results of a phase Ib dose-escalation study. J Clin Oncol 2013; 31: e13518-e13518.
[129] Krop IE, Saura C, Rodon Ahnert J, Becerra C, Britten CD, Baselga J. A phase I/IB dose-escalation study of BEZ235 in combination with trastuzumab in patients with PI3-kinase or PTEN altered HER2+ metastatic breast cancer. ASCO Meet Abstr 2012; 30: 508.
[130] Hall CP, Reynolds CP, Kang MH. Modulation of glucocorticoid resistance in pediatric T-cell acute lymphoblastic leukemia by increasing BIM expression with the PI3K/mTOR Inhibitor BEZ235. Clin Cancer Res 2016; 22: 621-32.
[131] Aalipour A, Advani RH. Bruton tyrosine kinase inhibitors: a promising novel targeted treatment for B cell lymphomas. Br J Haematol 2013; 163: 436-43.
[132] Aalipour A, Advani RH. Bruton's tyrosine kinase inhibitors and their clinical potential in the treatment of B-cell malignancies: focus on ibrutinib. Ther Adv Hematol 2014; 5: 121-33.
[133] Kim E, Hurtz C, Koehrer S, Wang Z, Balasubramanian S, Burger JA. Ibrutinib inhibits pre-BCR+B-cell acute lymphoblastic leukemia progression by targeting BTK and BLK. Blood 2017; 129: 1155-65.
[134] Roskoski R. Ibrutinib inhibition of Bruton protein-tyrosine kinase (BTK) in the treatment of B cell neoplasms. Pharmacol Res 2016; 113: 395-408.
[135] Schwartzman O, Savino AM, Gombert M, Palmi C, Cario G, Izraeli S. Suppressors and activators of JAK-STAT signaling at diagnosis and relapse of acute lymphoblastic leukemia in down syndrome. Proc Natl Acad Sci U S A 2017; 114: E4030-9.
[136] Qin H, Cho M, Haso W, Zhang L, Tasian SK, Fry TJ. Eradication of B-ALL using chimeric antigen receptor-expressing T cells targeting the TSLPR oncoprotein. Blood 2015; 126: 629-39.
[137] Savino AM, Sarno J, Trentin L, Vieri M, Fazio G, Cazzaniga G. The histone deacetylase inhibitor givinostat (ITF2357) exhibits potent anti-tumor activity against CRLF2-rearranged BCP-ALL. Leukemia 2017; 31: 2365-75.
[138] Verstraete K, Peelman F, Braun H, Lopez J, Van Rompaey D, Dansercoer A, Vandenberghe I, Pauwels K, Tavernier J, Lambrecht BN, Hammad H, De Winter H, Beyaert R, Lippens G, Savvides SN. Structure and antagonism of the receptor complex mediated by human TSLP in allergy and asthma. Nat Commun 2017; 8: 14937.
[139] Irving J, Matheson E, Minto L, Blair H, Case M, Eckert C. Ras pathway mutations are prevalent in relapsed childhood acute lymphoblastic leukemia and confer sensitivity to MEK inhibition. Blood 2014; 124: 3420-30.
[140] Canté-Barrett K, Spijkers-Hagelstein JA, Buijs-Gladdines JG, Uitdehaag JC, Smits WK, Meijerink JP. MEK and PI3K-AKT inhibitors synergistically block activated IL7 receptor signaling in T-cell acute lymphoblastic leukemia. Leukemia 2016; 30: 1832-43.
[141] Armstrong SA, Kung AL, Mabon ME, Silverman LB, Stam RW, Korsmeyer SJ. Inhibition of FLT3 in MLL: validation of a therapeutic target identified by gene expression based classification. Cancer Cell 2003; 3: 173-83.
[142] Armstrong SA, Mabon ME, Silverman LB, Li A, Gribben JG, Korsmeyer SJ. FLT3 mutations in childhood acute lymphoblastic leukemia. Blood 2004; 103: 3544-6.
[143] Bai XT, Moles R, Chaib-Mezrag H. Small PARP inhibitor PJ-34 induces cell cycle arrest and apoptosis of adult T-cell leukemia cells. J Hematol Oncol 2015; 8: 1-12.
[144] Nakahara T, Kita A, Yamanaka K, Mori M, Amino N, Sasamata M. Broad spectrum and potent antitumor activities of YM155, a novel small-molecule survivin suppressant, in a wide variety of human cancer cell lines and xenograft models. Cancer Sci 2011; 102: 614-21.
[145] Khan Z, Khan AA, Yadav H, Prasad GB, Bisen PS. Survivin, a molecular target for therapeutic interventions in squamous cell carcinoma. Cell Mol Biol Lett 2017; 22: 8.
[146] Troeger A, Siepermann M, Escherich G, Meisel R, Willers R, Dilloo D. Survivin and its prognostic significance in pediatric acute B-cell precursor lymphoblastic leukemia. Haematologica 2007; 92: 1043-50.
[147] Chang BH, Johnson K, LaTocha D, Rowley JS, Bryant J, Tyner JW. YM155 potently kills acute lymphoblastic leukemia cells through activation of the DNA damage pathway. J Hematol Oncol 2015; 8: 39.
[148] Vogler M, Walter HS, Dyer MJ. Targeting anti-apoptotic BCL2 family proteins in haematological malignancies - from pathogenesis to treatment. Br J Haematol 2017; 178: 364-79.
[149] Suryani S, Carol H, Chonghaile TN, Frismantas V, Sarmah C, High L, Bornhauser B, Cowley MJ, Szymanska B, Evans K, Boehm I, Tonna E, Jones L, Manesh DM, Kurmasheva RT, Billups C, Kaplan W, Letai A, Bourquin JP, Houghton PJ, Smith MA, Lock RB. Cell and molecular determinants of in vivo efficacy of the BH3 mimetic ABT-263 against pediatric acute lymphoblastic leukemia xenografts. Clin Cancer Res 2014; 20: 4520-31.
[150] Benito JM, Godfrey L, Kojima K, Hogdal L, Wunderlich M, Konopleva M. MLL-rearranged acute lymphoblastic leukemias activate BCL-2 through H3K79 methylation and are sensitive to the BCL-2-Specific antagonist ABT-199. Cell Rep 2015; 13: 2715-27.
[151] Akahane K, Sanda T, Mansour MR, Radimerski T, Deangelo DJ, Look AT. HSP90 inhibition leads to degradation of the TYK2 kinase and

apoptotic cell death in T-cell acute lymphoblastic leukemia. Leukemia 2016; 30: 219-28.
[152] Annesley CE, Brown P. Novel agents for the treatment of childhood acute leukemia. Ther Adv Hematol 2015; 6: 61-79.
[153] Cortes J, Thomas D, Koller C, Giles F, Estey E, Kantarjian H. Phase I study of bortezomib in refractory or relapsed acute leukemias. Clin Cancer Res 2004; 10: 3371-6.
[154] Horton TM, Pati D, Plon SE, Thompson PA, Bomgaars LR, Adamson PC, Ingle AM, Wright J, Brockman AH, Paton M, Blaney SM. A phase 1 study of the proteasome inhibitor bortezomib in pediatric patients with refractory leukemia: a children's oncology group study. Clin Cancer Res 2007; 13: 1516-22.
[155] Messinger YH, Gaynon PS, Sposto R, Van Der Giessen J, Eckroth E, Bostrom BC. Bortezomib with chemotherapy is highly active in advanced B-precursor acute lymphoblastic leukemia: Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) Study. Blood 2012; 120: 285-90.
[156] Horton TM, Gannavarapu A, Blaney SM, D'Argenio DZ, Plon SE, Berg SL. Bortezomib interactions with chemotherapy agents in acute leukemia in vitro. Cancer Chemother Pharmacol 2006; 58: 13-23.
[157] Horton T, Lu X, O'Brien M. Bortezomib reinduction therapy to improve response rates in pediatric ALL in first relapse: a children's oncology group (COG) study (AALL07P1). ASCO Annu. Meet., 2013. pp. Abstract 10003.
[158] Bhatla T, Wang J, Morrison DJ, Raetz EA, Burke MJ, Carroll WL. Epigenetic reprogramming reverses the relapse-specific gene expression signature and restores chemosensitivity in childhood B-lymphoblastic leukemia. Blood 2012; 119: 5201-10.
[159] Jabbour E, Brien SO, Ravandi F, Kantarjian H. Monoclonal antibodies in acute lymphoblastic leukemia. Blood 2015; 125: 4010-7.
[160] McLaughlin P, Hagemeister FB, Grillo-López AJ. Rituximab in indolent lymphoma: the single-agent pivotal trial. Semin Oncol 1999; 26: 79-87.
[161] Maury S, Chevret S, Thomas X, Heim D, Leguay T, Dombret H. Rituximab in B-lineage adult acute lymphoblastic leukemia. N Engl J Med 2016; 375: 1044-53.
[162] Jabbour E, Kantarjian H. Immunotherapy in adult acute lymphoblastic leukemia: the role of monoclonal antibodies. Blood Adv 2016; 1: 260-4.
[163] Lemery SJ, Zhang J, Rothmann MD, Yang J, Earp J, Pazdur R. U.S. food and drug administration approval: ofatumumab for the treatment of patients with chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab. Clin Cancer Res 2010; 16: 4331-8.
[164] Thomas DA, O'Brien S, Jorgensen JL, Cortes J, Faderl S, Kantarjian HM. Prognostic significance of CD20 expression in adults with de novo precursor B-lineage acute lymphoblastic leukemia. Blood 2009; 113: 6330-7.
[165] Beers SA, French RR, Chan HT, Lim SH, Jarrett TC, Cragg MS. Antigenic modulation limits the efficacy of anti-CD20 antibodies: implications for antibody selection. Blood 2010; 115: 5191-201.
[166] Jabbour E, Kantarjian HM, Thomas DA, Sasaki K, Garcia-Manero G, Garris R, Cortes JE, Kadia TM, Ravandi F, Verstovsek S, O'Brien S. Phase II study of the hyper-cvad regimen in combination with ofatumumab as frontline therapy for adults with CD-20 positive acute lymphoblastic leukemia (ALL). Blood 2014; 124: 5277.
[167] Awasthi A, Ayello J, Van De Ven C, Elmacken M, Barth MJ, Cairo MS. Obinutuzumab versus rituximab significantly enhances apoptosis and ADCC in vitro and overall survival in vivo of rituximab sensitive/resistant burkitt lymphoma (BL). Br J Haematol 2015; 171: 83.
[168] Schlegel P, Lang P, Zugmaier G, Ebinger M, Kreyenberg H, Handgretinger R. Pediatric post-transplant relapsed/refractory B-precursor acute lymphoblastic leukemia shows durable remission by therapy with the T-cell engaging bispecific antibody blinatumomab. Haematologica 2014; 99: 1212-9.
[169] Topp MS, Gökbuget N, Stein AS, Zugmaier G, O'Brien S, Kantarjian HM. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015; 16: 57-66.
[170] Topp MS, Kufer P, Go N, Degenhard E, Ko R, Bargou RC. Targeted therapy with the t-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-Lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol 2011; 29: 2493-8.
[171] Gökbuget N, Dombret H, Bonifacio M, Reichle A, Graux C, Bargou RC. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 2018; 131: 1522-1531.
[172] Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Topp MS. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017; 376: 836-47.
[173] Van Epps HA, Heiser R, Cao A. Denintuzumab mafodotin stimulates immune responses and synergizes with CD20 antibodies to heighten anti-tumor activity in preclinical models of non-hodgkin lymphoma. Am Soc Hematol Annu Meet Expo 2016; Abstract 4177.

[174] Fathi A, Borate U, DeAngelo DJ OM. A phase 1 study of denintuzumab mafodotin (SGN-CD19A) in adults with relapsed or refractory B-Lineage acute leukemia (B-ALL) and highly aggressive lymphoma. Blood 2015; 126: 1328.

[175] Zammarchi F, Williams DG, Adams L, Tyrer PC, Mellinas-Gomez M, Havenith K, Chivers S, D'Hooge F, Howard1 PW, Hartley JA, H van Berkel P. Pre-clinical development of ADCT-402, a novel pyrrolobenzodiazepine (PBD)-based antibody drug conjugate (ADC) targeting cd19-expressing B-cell malignancies. Blood 2015; 126: 1564.

[176] Vallera DA, Todhunter DA, Kuroki DW, Shu Y, Sicheneder A, Chen H. A bispecific recombinant immunotoxin, DT2219, targeting human CD19 and CD22 receptors in a mouse xenograft model of B-cell leukemia/lymphoma. Clin Cancer Res 2005; 11: 3879-88.

[177] Vallera DA, Chen H, Sicheneder AR, Panoskaltsis-Mortari A, Taras EP. Genetic alteration of a bispecific ligand-directed toxin targeting human CD19 and CD22 receptors resulting in improved efficacy against systemic B cell malignancy. Leuk Res 2009; 33: 1233-42.

[178] Bachanova V, Frankel AE, Cao Q, Lewis D, Grzywacz B, Vallera DA. Phase i study of a bispecific ligand-directed toxin targeting CD22 and CD19 (DT2219) for refractory B-cell malignancies. Clin Cancer Res 2015; 21: 1267-72.

[179] Sullivan-Chang L, O'Donnell RT, Tuscano JM. Targeting CD22 in B-cell malignancies: current status and clinical outlook. BioDrugs 2013; 27: 293-304.

[180] Shah N, Stevenson MS, Yuan CS, Richards K, Delbrook C, Kreitman RJ, Pastan I, Wayne AS. Characterization of CD22 expression in acute lymphoblastic leukemia. Pediatr 2015; 62: 964-9.

[181] DiJoseph JF, Armellino DC, Boghaert ER, Khandke K, Dougher MM, Damle NK. Antibody-targeted chemotherapy with CMC-544: a CD22-targeted immunoconjugate of calicheamicin for the treatment of B-lymphoid malignancies. Blood 2004; 103: 1807-14.

[182] Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Advani AS. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med 2016; 375: 740-53.

[183] Kreitman RJ, Pastan I. Antibody fusion proteins: anti-CD22 recombinant immunotoxin moxetumomab pasudotox. Clin Cancer Res 2011; 17: 6398-405.

[184] Kantarjian HM, Lioure B, Kim SK, Atallah E, Leguay T, Dombret H. A phase II study of coltuximab ravtansine (SAR3419) monotherapy in patients with relapsed or refractory acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk 2016; 16: 139-45.

[185] Raetz EA, Cairo MS, Borowitz MJ, Lu X, Devidas M, Reid JM, Goldenberg DM, Wegener WA, Zeng H, Whitlock JA, Adamson PC, Hunger SP, Carroll WL. Re-induction chemoimmunotherapy with epratuzumab in relapsed acute lymphoblastic leukemia (ALL): phase II results from children's oncology group (COG) study ADVL04P2. Pediatr Blood Cancer 2015; 62: 1171-5.

[186] Advani AS, Mcdonough S, Coutre S, Wood B, Radich J, Appelbaum FR. SWOG S0910: a phase 2 trial of clofarabine/cytarabine/epratuzumab for relapsed/refractory acute lymphocytic leukaemia. Br J Haematol 2014; 165: 504-9.

[187] Hu Y, Turner MJ, Shields J, Gale MS, Hutto E, Kaplan JM. Investigation of the mechanism of action of alemtuzumab in a human CD52 transgenic mouse model. Immunology 2009; 128: 260-70.

[188] Batlevi CL, Matsuki E, Brentjens RJ, Younes A. Novel immunotherapies in lymphoid malignancies. Nat Rev Clin Oncol 2016; 13: 25-40.

[189] Kochenderfer JN, Rosenberg SA. Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. Nat Rev Clin Oncol 2013; 10: 267-76.

[190] Maher J, Brentjens RJ, Gunset G, Rivière I, Sadelain M. Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRζ/CD28 receptor. Nat Biotechnol 2002; 20: 70-5.

[191] Imai C, Mihara K, Andreansky M, Nicholson IC, Pui CH, Campana D. Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia. Leukemia 2004; 18: 676-84.

[192] Maude SL, Teachey DT, Porter DL, Grupp SA. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Blood 2015; 125: 4017-23.

[193] Savoldo B, Ramos CA, Liu E, Mims MP, Keating MJ, Dotti G. CD28 costimulation improves expansion and persistence of chimeric antigen receptor-modified T cells in lymphoma patients. J Clin Invest 2011; 121: 1822-6.

[194] Brentjens RJ, Latouche JB, Santos E, Marti F, Gong MC, Sadelain M. Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15. Nat Med 2003; 9: 279-86.

[195] Brentjens RJ, Rivière I, Park JH, Davila ML, Wang X, Sadelain M. Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias. Blood 2011; 118: 4817-28.

[196] Davila ML, Riviere I, Wang X, Bartido S, Park J, Brentjens R. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med 2014; 6.

[197] Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Mackall CL. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015; 385: 517-28.
[198] Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, Chew A, Gonzalez VE, Zheng Z, Lacey SF, Mahnke YD, Melenhorst JJ, Rheingold SR, Shen A, Teachey DT, Levine BL, June CH, Porter DL, Grupp SA. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014; 371: 1507-17.
[199] Kochenderfer JN, Dudley ME, Feldman SA, Wilson WH, Spaner DE, Rosenberg SA. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. Blood 2012; 119: 2709-20.
[200] Di Stasi A, Tey SK, Dotti G, Fujita Y, Kennedy-Nasser A, Brenner MK. Inducible apoptosis as a safety switch for adoptive cell therapy. N Engl J Med 2011; 365: 1673-83.
[201] Gargett T, Brown MP. The inducible caspase-9 suicide gene system as a "safety switch" to limit on-target, off-tumor toxicities of chimeric antigen receptor T cells. Front Pharmacol 2014; 5: 235.
[202] Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, Sommermeyer D, Melville K, Pender B, Budiarto TM, Robinson E, Steevens NN, Chaney C, Soma L, Chen X, Yeung C, Wood B, Li D, Cao J, Heimfeld S, Jensen MC, Riddell SR, Maloney DG. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest 2016; 126: 2123-38.
[203] Wei G, Wang J, Huang H, Zhao Y. Novel immunotherapies for adult patients with B-lineage acute lymphoblastic leukemia. J Hematol Oncol 2017; 10: 150.
[204] Lacey SF, Xu J, Ruella M, Barrett DM, Kulikovskaya I, Melenhorst JJ. Cars in leukemia: relapse with antigen-negative leukemia originating from a single B cell expressing the leukemia-targeting CAR. Blood 2016; 128: 281 LP-281.
[205] Long AH, Haso WM, Orentas RJ. Lessons learned from a highly-active CD22-specific chimeric antigen receptor. Oncoimmunology 2013; 2: e23621.
[206] Haso W, Lee DW, Shah NN, Stetler-Stevenson M, Yuan CM, Orentas RJ. Anti-CD22-chimeric antigen receptors targeting B-cell precursor acute lymphoblastic leukemia. Blood 2013; 121: 1165-1174.
[207] Shah NN, Stetler-Stevenson M, Yuan CM, Shalabi H, Yates B, Fry TJ. Minimal residual disease negative complete remissions following anti-CD22 chimeric antigen receptor (CAR) in children and young adults with relapsed/refractory acute lymphoblastic leukemia (ALL). Blood 2016; 128: 650.
[208] Rossig C, Pule M, Altvater B, Saiagh S, Wright G, Amrolia P. Vaccination to improve the persistence of CD19CAR gene- modified T cells in relapsed pediatric acute lymphoblastic leukemia. Leukemia 2017; 31: 1087-109539.
[209] Kebriaei P, Singh H, Huls MH, Figliola MJ, Bassett R, Olivares S, Jena B, Dawson MJ, Kumaresan PR, Su S, Maiti S, Dai J, Moriarity B, Forget MA, Senyukov V, Orozco A, Liu T, McCarty J, Jackson RN, Moyes JS, Rondon G, Qazilbash M, Ciurea S, Alousi A, Nieto Y, Rezvani K, Marin D, Popat U, Hosing C, Shpall EJ, Kantarjian H, Keating M, Wierda W, Do KA, Largaespada DA, Lee DA, Hackett PB, Champlin RE, Cooper LJ. phase I trials using sleeping beauty to generate CD19-specific CAR T cells. J Clin Invest 2016; 126: 3363-76.
[210] Fielding AK. Current therapeutic strategies in adult acute lymphoblastic leukemia. Hematol Oncol Clin North Am 2011; 25: 1255-79.
[211] Uludağ H, Landry B, Valencia-Serna J, Remant-Bahadur KC, Meneksedağ-Erol D. Current attempts to implement siRNA-based RNAi in leukemia models. Drug Discov Today 2016; 21: 1412-20.
[212] Iorns E, Lord CJ, Turner N, Ashworth A. Utilizing RNA interference to enhance cancer drug discovery. Nat Rev Drug Discov 2007; 6: 556-68.
[213] Rossbach M. Small non-coding RNAs as novel therapeutics. Curr Mol Med 2010; 10: 361-8.
[214] Montazeri Aliabadi H, Mahdipoor P, Kucharsky C, Chan N, Uludag H. Effect of siRNA pre-exposure on subsequent response to siRNA therapy. Pharm Res 2015; 32: 3813-26.
[215] Ansari AS, Santerre PJ, Uludağ H. Biomaterials for polynucleotide delivery to anchorage-independent cells. J Mater Chem B 2017; 5: 7238-61.
[216] Abbasi M, Lavasanifar A, Uludag H. Recent attempts at RNAi-mediated P-glycoprotein down-regulation for reversal of multidrug resistance in cancer. Med Res Rev 2013; 33: 33-53.
[217] Landry B, Valencia-Serna J, Gul-Uludag H, Jiang X, Janowska-Wieczorek A, Brandwein J, Uludag H. Progress in RNAi-mediated molecular therapy of acute and chronic myeloid leukemia. Mol Ther Nucleic Acids 2015; 4: e240.
[218] Uckun FM, Ma H, Cheng J, Myers DE, Qazi S. CD22ΔE12 as a molecular target for RNAi therapy. Br J Haematol 2015; 169: 401-14.
[219] Uckun FM, Qazi S, Ma H, Yin L, Cheng J. A rationally designed nanoparticle for RNA interference therapy in B-lineage lymphoid malignancies. EBioMedicine 2014; 1: 141-55.
[220] Gruhn B, Naumann T, Gruner D, Walther M, Wittig S, Sonnemann J. The expression of histone deacetylase 4 is associated with prednisone poor-response in childhood acute lymphoblastic leukemia. Leuk Res 2013; 37: 1200-7.

[221] Grandori C, Cowley SM, James LP, Eisenman RN. The Myc/Max/Mad network and the transcriptional control of cell behavior. Annu Rev Cell Dev Biol 2000; 16: 653-99.
[222] Barisone GA, Yun JS, Díaz E. From cerebellar proliferation to tumorigenesis: new insights into the role of Mad3. Cell Cycle 2008; 7: 423-7.
[223] Satake N, Duong C, Chen C, Barisone GA, Diaz E, Nitin N. Targeted therapy with MXD3 siRNA, anti-CD22 antibody and nanoparticles for precursor B-cell acute lymphoblastic leukaemia. Br J Haematol 2014; 167: 487-99.
[224] Barisone GA, Satake N, Lewis C, Duong C, Chen C, Díaz E. Loss of MXD3 induces apoptosis of Reh human precursor B acute lymphoblastic leukemia cells. Blood Cells Mol Dis 2015; 54: 329-35.
[225] Satake N, Duong C. Novel targeted therapy for precursor B-cell acute lymphoblastic leukemia: anti-CD22 antibody-MXD3 antisense oligonucleotide conjugate. Mol Med 2016; 22: 1.
[226] Cerny-Reiterer S, Meyer RA, Herrmann H, Peter B, Gleixner KV, Valent P. Identification of heat shock protein 32 (Hsp32) as a novel target in acute lymphoblastic leukemia. Oncotarget 2014; 5: 1198-211.
[227] Hynes RO. Integrins: bidirectional, allosteric signaling machines. Cell 2002; 110: 673-87.
[228] Shishido S, Bönig H, Kim YM. Role of integrin alpha4 in drug resistance of leukemia. Front Oncol 2014; 4: 99.
[229] Duchartre Y, Bachl S, Kim HN, Gang EJ, Lee S, Liu HC, Shung K, Xu R, Kruse A, Tachas G, Bonig H, Kim YM. Effects of CD49d-targeted antisense-oligonucleotide on α4 integrin expression and function of acute lymphoblastic leukemia cells: results of in vitro and in vivo studies. PLoS One 2017; 12: e0187684.
[230] Jyotsana N, Sharma A, Chaturvedi A, Scherr M, Kuchenbauer F, Heuser M. RNA interference efficiently targets human leukemia driven by a fusion oncogene in vivo. Leukemia 2018; 32: 224-226.
[231] Fischer U, Forster M, Rinaldi A, Risch T, Sungalee S, Warnatz HJ, Bornhauser B, Gombert M, Kratsch C, Stütz AM, Sultan M, Tchinda J, Worth CL, Amstislavskiy V, Badarinarayan N, Baruchel A, Bartram T, Basso G, Canpolat C, Cario G, Cavé H, Dakaj D, Delorenzi M, Dobay MP, Eckert C, Ellinghaus E, Eugster S, Frismantas V, Ginzel S, Haas OA, Heidenreich O, Hemmrich-Stanisak G, Hezaveh K, Höll JI, Hornhardt S, Husemann P, Kachroo P, Kratz CP, Te Kronnie G, Marovca B, Niggli F, McHardy AC, Moorman AV, Panzer-Grümayer R, Petersen BS, Raeder B, Ralser M, Rosenstiel P, Schäfer D, Schrappe M, Schreiber S, Schütte M, Stade B, Thiele R, von der Weid N, Vora A, Zaliova M, Zhang L, Zichner T, Zimmermann M, Lehrach H, Borkhardt A, Bourquin JP, Franke A, Korbel JO, Stanulla M, Yaspo ML. Genomics and drug profiling of fatal TCF3-HLF-positive acute lymphoblastic leukemia identifies recurrent mutation patterns and therapeutic options. Nat Genet 2015; 47: 1020-9.
[232] Ouimet M, Drouin S, Lajoie M, Caron M, St-Onge P, Sinnett D. A childhood acute lymphoblastic leukemia-specific lncRNA implicated in prednisolone resistance, cell proliferation, and migration. Oncotarget 2017; 8: 7477-88.
[233] Yeoh EJ, Ross ME, Shurtleff SA, Williams WK, Patel D, Downing JR. Classification, subtype discovery, and prediction of outcome in pediatric acute lymphoblastic leukemia by gene expression profiling. Cancer Cell 2002; 1: 133-43.
[234] Fernando TR, Rodriguez-Malave NI, Waters EV, Yan W, Casero D, Rao DS. LncRNA expression discriminates karyotype and predicts survival in B-lymphoblastic leukemia. Mol Cancer Res 2015; 13: 839-51.
[235] Wang Y, Wu P, Lin R, Rong L, Xue Y, Fang Y. LncRNA NALT interaction with NOTCH1 promoted cell proliferation in pediatric T cell acute lymphoblastic leukemia. Sci Rep 2015; 5: 13749.
[236] Meade BR, Gogoi K, Hamil AS, Palm-Apergi C, Van Den Berg A, Dowdy SF. Efficient delivery of RNAi prodrugs containing reversible charge-neutralizing phosphotriester backbone modifications. Nat Biotechnol 2014; 32: 1256-61.
[237] Daub H, Specht K, Ullrich A. Strategies to overcome resistance to targeted protein kinase inhibitors. Nat Rev Drug Discov 2004; 3: 1001-10.
[238] Takaki T, Trenz K, Costanzo V, Petronczki M. Polo-like kinase 1 reaches beyond mitosis-cytokinesis, DNA damage response, and development. Curr Opin Cell Biol 2008; 20: 650-60.
[239] Kolosenko I, Edsbäcker E, Björklund AC, Hamil AS, Goroshchuk O, Palm-Apergi C. RNAi prodrugs targeting Plk1 induce specific gene silencing in primary cells from pediatric T-acute lymphoblastic leukemia patients. J Control Release 2017; 261: 199-206.
[240] Ikezoe T, Yang J, Nishioka C, Takezaki Y, Tasaka T, Yokoyama A. A novel treatment strategy targeting polo-like kinase 1 in hematological malignancies. Leukemia 2009; 23: 1554-76.
[241] Campana D. Minimal residual disease in acute lymphoblastic leukemia. Hematology 2010; 2010: 7-12.
[242] Minieri V, De Dominici M, Porazzi P, Mariani SA, Spinelli O, Rambaldi A, Peterson LF, Porcu P, Nevalainen MT, Calabretta B. Targeting STAT5 or STAT5-reulated pathways suppresses leukemogenesis of Ph^+ acute lymphoblastic leukemia. Molec Cell Biol 2018; 78: 5791-5807.
[243] Janz LE T. Childhood cancer incidence and mortality in Canada. Stat Canada Heal a Glance 2015.