Emerging molecular subtypes and therapeutic targets in B-cell precursor acute lymphoblastic leukemia

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Abstract B-cell precursor acute lymphoblastic leukemia (BCP-ALL) is characterized by genetic alterations with high heterogeneity. Precise subtypes with distinct genomic and/or gene expression patterns have been recently revealed using high-throughput sequencing technology. Most of these profiles are associated with recurrent non-overlapping rearrangements or hotspot point mutations that are analogous to the established subtypes, such as *DUX4* rearrangements, *MEF2D* rearrangements, *ZNF384/ZNF362* rearrangements, *NUTM1* rearrangements, *BCL2/MYC* and/or *BCL6* rearrangements, *ETV6-RUNX1*-like gene expression, *PAX5alt* (diverse *PAX5* alterations, including rearrangements, intragenic amplifications, or mutations), and hotspot mutations *PAX5* (p.Pro80Arg) with biallelic *PAX5* alterations, *IKZF1* (p.Asn159Tyr), and *ZEB2* (p.His1038Arg). These molecular subtypes could be classified by gene expression patterns with RNA-seq technology. Refined molecular classification greatly improved the treatment strategy. Multiagent therapy regimens, including target inhibitors (e.g., imatinib), immunomodulators, monoclonal antibodies, and chimeric antigen receptor T-cell (CAR-T) therapy, are transforming the clinical practice from chemotherapy drugs to personalized medicine in the field of risk-directed disease management. We provide an update on our knowledge of emerging molecular subtypes and therapeutic targets in BCP-ALL.

Keywords BCP-ALL; subtypes; translocation; aneuploidy; sequence mutations

Introduction

B-cell precursor acute lymphoblastic leukemia (BCP-ALL) is a blood cancer that originates from B-lymphoid progenitors [1,2]. Genetic susceptibility and somatic clonal expansion (tumor acquired) are the hallmarks and biological basis of BCP-ALL. The enrichment of chromosomal alterations, including genomic translocations and entire chromosome losses or gains (aneuploidy), DNA copy number variations (CNVs), and sequence mutations, are common in leukemic blast cells of BCP-ALLs [3–7]. In the past few years, numerous molecular subtypes with distinct genetic abnormalities and clinical significance have been identified in multicenter, global collaboration

cohort studies of patients with BCP-ALL [8–12]. A recognition of these multifaceted genetic alterations contributing to leukemogenesis is vital in ensuring a precise risk stratification of the disease, which can then lead to improvements to cure rates in both adults and children with BCP-ALL [5,12–26]. Before the 1980s, with the combined effectiveness of health-care systems and the absence of actionable risk stratification factors, the five-year overall survival rate was only approximately 50% in children patients with BCP-ALL [27–29]. In recent years, the released data from multiple large-cohort clinical trials indicate a five-year overall survival rate that is higher than 90% in children [29–42]. In addition, the rapid advancement in new drugs and agents, including target inhibitors, i.e., tyrosine kinase inhibitors (TKIs) and epigenetic inhibitors, immunomodulators, monoclonal antibodies, and chimeric antigen receptor T-cells (CAR-T), may further improve the prognosis of relapsed or refractory (R/R) BCP-ALL [13,43].

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Overview of well-established molecular subtypes in BCP-ALL

The translocation t(9;22)(q34;q11.2) resulting in *BCR-ABL1* (Philadelphia, Ph) fusion accounted for 15%–25% of adults and 2%–5% of children with BCP-ALL [8,9,44]. *BCR-ABL1* fusion proteins are considered to be signaling regulators and can trigger kinase pathway activation [45–48]. Targeted treatments with TKIs have significantly improved the prognosis of patients with *BCR-ABL1* [8,9,13,49,50]. *KMT2A* (*MLL*) rearrangements account for 3%–4% of children with BCP-ALL, particularly in infants (< 1 year old), and in 4%–10% of adult patients, mainly > 30 years old, with BCP-ALL [8,9,18,24,51,52]. Additionally, this rearrangement is typically associated with poor prognosis [24,52,53]. The translocations t(4;11)(q21;q23), t(11;19)(q23;p13.3), and t(9;11)(p21;q23) resulting in *KMT2A-AFF1*, *KMT2A-MLLT1*, and *KMT2A-MLLT3*, respectively, account for more than 90% of *KMT2A* fusions in BCP-ALL [8,9]. The translocation t(12;21)(p13;q22) resulting in *ETV6-RUNX1* (also known as *TEL-AML1*) comprises approximately 15%–25% of children with BCP-ALL [8,9,17,18]. However, adults (< 1%) and patients with *ETV6-RUNX1* rarely have the same sensitivity to chemotherapy, and relapse and death events are less common [5,8,9,17,54,55]. In addition, *ETV6-RUNX1* fusion is detectable in 5% healthy newborns based on DNA-based genomic inverse PCR for exploration of ligated breakpoint screening, but most never transform to BCP-ALL [56]. Transcription factor 3 (*TCF3*) is frequently involved in two types of translocations, namely, t(1;19)(q23;p13) and t(17;19)(q22;p13), which result in *TCF3-PBX1* and *TCF3-HLF* fusions, respectively. *TCF3-PBX1* accounts for approximately 4%–7% of children patients and 2%–5% of adult patients with BCP-ALL and is associated with intermediate outcomes [8,9,12,54]. *TCF3-HLF* is a rare gene fusion (< 1% of ALL), and relapse and death events are common [25,57]. *HLF* is also involved in translocation t(18;19)(q21;p13), thereby resulting in *TCF4-HLF*. Both *TCF3-HLF* and *TCF4-HLF* fusions retain the bZIP_2 domain and accompany the overexpression of *HLF* [8,9,25]. The complex intrachromosomal amplification of chromosome 21 (iAMP21), which was first reported in 2003, helped to define a distinct cytogenetic subgroup [58,59]. This amplification occurs in approximately 2%–3% of children with B-lineage ALL, especially in adolescence [5,9,12]. This condition was originally considered a rare, high-risk subtype of BCP-ALL, but current intensive therapy has greatly improved its outcome [59,60]. High hyperdiploidy with a gain of at least five chromosomes is another independent predictor (along with *ETV6-RUNX1*) of favorable outcomes and accounts for approximately 15%–25% of patients with childhood BCP-ALL. However, high hyperdiploidy is rare in adults (< 1%) [8,9].

Conversely, hypodiploid (< 44 chromosomes) is uncommon (2%–3%) and associated with inferior outcomes compared with high hyperdiploidy BCP-ALL. In addition, hypodiploid (< 44 chromosomes) is heterogeneous with distinct genetic abnormalities and gene expression profiles consisting of near-haploid BCP-ALL (25–29 chromosomes), low hypodiploid (32–39 chromosomes), and high hypodiploid (40–43 chromosomes) (Table 1) [5,12,23].

The well-established molecular subtypes of BCP-ALL have been mostly integrated into the guidance of therapy options (e.g., dose and times of chemotherapy and types of targeted drugs) [13]. Their integration has significantly improved the long-term survival of both adult and children patients. However, subtypes with poor/intermediate prognosis, including *BCR-ABL1*, *KMT2A* fusions, *TCF3-PBX1*, *HLF* fusions, and low hypodiploid, are needed in intensive chemotherapy [5]. *BCR-ABL1* and *KMT2A* fusions not only occur in BCP-ALL but also in other types of acute or chronic leukemia, including acute myeloid leukemia (AML), mixed phenotype acute leukemia (MPAL), and chronic myeloid leukemia [61–63]. A potential supposition is that the fusion of genes may occur at different stages of hematopoietic stem cell development.

Emerging molecular subtypes in BCP-ALL

DUX4, *MEF2D*, and *ZNF384* gene fusions

Three new subtypes of adult and childhood BCP-ALL have been described recently [16,18,20–22,64]. The subtypes are involved in the rearrangements of DNA binding factors, including double homeobox 4 gene (*DUX4*), myocyte enhancer factor 2D (*MEF2D*), and zinc finger protein 384 (*ZNF384*), which separately account for approximately 4%–7%, 2%–4%, and 3%–5% of childhood BCP-ALL and 4%–7%, 2%–7%, and 3%–8% of adult BCP-ALL [8,9,15–18,20–22,26,65–67]. *DUX4-r*, *ZNF384-r*, and *MEF2D-r* BCP-ALL are associated with favorable, intermediate, and poor diagnoses, respectively. In most patients, *DUX4* overexpression is the consequence of *DUX4* fusion, typically *IGH* but rarely *ERG* [17,20,21]. By contrast, the partner genes of *MEF2D* and *ZNF384* are complex and diverse. A total of 9 genes (*BCL9*, *SS18*, *FOXJ2*, *CSF1R*, *DAZAP1*, *STAT6*, *HNRNPUL1*, *HNRNP1*, and *HNRNPM*) and 11 genes (*EP300*, *TCF3*, *TAF15*, *CREBBP*, *EWSR1*, *ARID1B*, *SMARCA2*, *SMARCA4*, *SYNRG*, *NIPBL*, and *CLTC*) have been reported as fusion partners of *MEF2D* and *ZNF384* [8,15–18,20,22,66–68], respectively. Translocations t(1;1)(q21;q22) and t(1;19)(q22;q13) resulting in *MEF2D-BCL9* and *MEF2D-HNRNPUL1*, respectively, are the top two items in *MEF2D-r* BCP-ALL, accounting for 70% and 15% of the cases. *EP300*, *TCF3*, and *TAF15* are the most common 5' genes rearranged to *ZNF384* with

translocations t(12;22)(p13;q13), t(12;19)(p13;p13), and t(12;17)(p13;q11), representing approximately 50%, 10%–20%, and 10% of *ZNF384* fusion-positive cases.

DUX4, located within a D4Z4 repeat array in the subtelomeric region of chromosome 4, is a key transcription factor regulating embryonic development and is not expressed in normal B-cells. *DUX4* can bind a large percentage of activated genes in early developing embryos and improve the accessibility of genes as early as the 2- to 4-cell stages [20,21,69,70]. Intragenic deletions of *ERG* were previously reported in approximately 5% of children with BCP-ALLs, but they were designated as the biological feature in *DUX4-r* cases [5,21]. Functional studies show that *DUX4* rearrangements, as an early initiating event in leukemogenesis, can bind to an intragenic region of *ERG* and cause the overexpression of ERGalt with a noncanonical first exon and transcript. Aberrant ERGalt preserves the DNA binding and transactivating domains and encodes a truncated C-terminal *ERG* protein. The transcriptional activity of wild-type *ERG* is inhibited by the ERGalt protein-transforming leukemic blast cells [5,20,21,71]. Interestingly, despite the presence of approximately 40%–50% of genetic alterations in *IKZF1* deletions related to poor outcomes in other subtypes with BCP-ALL [72], *DUX4-r* BCP-ALL can achieve excellent outcome [5,12,17,18,21]. Recent studies have reported that *IGH-DUX4* translocation occurs on the silenced *IGH* allele, thereby reducing the oncogenic stress of *DUX4*'s high-level expression. The *ERG* deletions have a positive impact on the prognosis (*ERG* deletion positive/negative: five-year EFS 93%/68%, $P = 0.022$; five-year OS 97%/75%, $P = 0.029$) [73,74].

MEF2D is a transcription factor that can specifically bind to the myocyte-specific enhancer factor 2 (MEF2) element 5'-YTA[AT](4)TAR-3'. It belongs to the MEF2 gene family that contributes to the differentiation of muscle and neural cells, cardiac morphogenesis, formation of blood vessels, growth factor responsiveness, survival of neuronal cells, and acute leukemia [75,76]. As a member of the MEF2 gene family, *MEF2C* is an activated oncogene in early T-cell precursor ALL, a subtype of high risk T-lineage ALL [12,77–82]. In 2005, *MEF2D-DAZAP1* was reported in the TS-2 cell line, as established from a three-year-old girl with ALL; it was found to contain t(1;19)(q23;p13.3) but was lacking the *TCF3-PBX1* fusion [83]. In 2016, multiple research groups who used RNA-seq recognized simultaneously the *MEF2D* fusion in a subgroup of patients with BCP-ALL [16,18,20,64]. These studies determined that *MEF2D* fusions can retain the MADS box domain required to mediate DNA binding with enhanced *MEF2D* transcriptional activity. The heterogeneous nuclear ribonucleoproteins, including HNRNPUL1, HNRNP1, and HNRNPM, are involved in *MEF2D-r* ALL [8,9,15]. These proteins can bind RNA and are associated with pre-mRNA processing in the

nucleus. Histone deacetylase 9 (*HDAC9*), a target gene of *MEF2D*, is significantly upregulated in *MEF2D-r* patients, providing an optional therapeutic strategy by using histone deacetylase inhibitors, such as panobinostat [5,16,18]. Staurosporine and venetoclax have recently been reported to be effective in inducing the caspase-dependent proteolysis of MEF2D-fusion proteins and apoptosis in MEF2D-fusion⁺ ALL cells [84].

ZNF384, also called *CIZ* or *NMP4*, can encode a C2H2-type zinc finger protein, whose function remains largely elusive, although it may function as a transcription factor. *ZNF384* fusions are often diagnosed as BCP-ALLs with an expression of cell surface markers of myeloid lineage (CD13 and CD33) or as B/myeloid (B/M) MPAL comprising approximately 50% of B/M MPAL [63]. In 2002, seven cases with *ZNF384-r* acute leukemia and recurrent *EWSR1-ZNF384* and *TAF15-ZNF384* were reported [85]. On the basis of large-cohort RNA-seq data analysis, *ZNF384*-positive patients with BCP-ALL were identified as a prognostic subtype with distinct gene expression features [8,9,16–18,20,22,65,66,86,87]. All *ZNF384* fusions keep their entire coding region. Cell apoptotic response, MAPK signaling, and JAK-STAT signaling pathways are significantly upregulated in this subtype [8,22]. Cardiotrophin-like cytokine factor 1 (*CLCF1*) is one of the most upregulated genes in *ZNF384-r* BCP-ALL that can bind to *CRLF1* to form a compound cytokine, thereby ultimately activating the JAK-STAT signaling pathway and B-cell proliferation *in vivo* [22,88]. In addition, up to 60% of patients with *ZNF384* fusions also show alterations in their signaling molecules, such as *NRAS* and *FLT3*, and 40% have epigenetic mutations, particularly *SETD1B*, *CREBBP*, and *EZH2*.

“Like” or “phenocopy” subtypes in BCP-ALL

Somatic mutations in the coding region and gene expression profile can help us recognize “like” or “phenocopy” subtypes that share similar gene expression features but lack consistent biomarkers. In recent years, several multi-omics and large-cohort studies have identified such subtypes, including Ph-like, *ETV6-RUNX1*-like, *KMT2A*-like, and *ZNF384*-like [8,9]. Integrated datasets showed that Ph-like and *ETV6-RUNX1*-like account for approximately 6%–15% and 2%–3% of children patients and 20%–25% and < 1% of adult patients with BCP-ALL. However, both *KMT2A*-like and *ZNF384*-like are rare (< 1%). Ph-like and *ETV6-RUNX1*-like are associated with poor and intermediate outcomes. The prognoses of *KMT2A*-like and *ZNF384*-like remain unclear because of limitation of sample size [8,9,12].

The Ph-like subtype is *BCR-ABL1* negative, but its gene expression feature is similar to that of *BCR-ABL1*-positive patients [89–93]. The Ph-like subtype was registered in the

2016 revision to the WHO classification of myeloid neoplasms and acute leukemia [19]. Rearrangements of *CRLF2* (e.g., *IGH-CRLF2* and *P2RY8-CRLF2* at approximately 30%–50%), *ABL1/ABL2* (10%), *JAK2* (10%), the erythropoietin receptor gene (*EPOR*, 5%–10%), and *PDGFRB* (5%) are the major chromosomal markers. Sequence mutations of signaling molecules, such as JAK-STAT signaling and Ras signaling (e.g., *NRAS*, *KRAS*, *JAK2*, and *PTPN11*), account for up to 15%–20% of Ph-like cases [8,9]. *BCR-ABL1* and Ph-like are associated with poor response to chemotherapy but are sensitive to TKIs, such as imatinib and dasatinib.

The *ETV6-RUNX1*-like subtype was defined as *ETV6-RUNX1* fusion negative and coexists with other *ETV6* and *IKZF1* alterations [17], accounting for approximately 10%–20% of the *ETV6-RUNX1*-like subtype. The *ETV6-RUNX1*-like subtype is also significantly enriched in children patients, and more than 80% of cases of *ETV6-RUNX1*-like subtype are children [8,9].

The *KMT2A*-like and *ZNF384*-like are recently defined subtypes, accounting for 5%–15% and 7%–10% of the *KMT2A*-like and *ZNF384*-like [8,9]. Rare fusions, such as *MED12-HOXA9* and *AFF1-TMEM156*, are found in *KMT2A*-like cases. Notably, *HOXA9* is deregulated in *KMT2A* fusion-positive patients, and *AFF1* is the most common partner gene in *KMT2A* fusions [8,9]. Recurrent *ZNF362* fusions (*SMARCA2-ZNF362* and *TAF15-ZNF362*) are found in *ZNF384*-like ALL. The fusion partner genes, including *SMARCA2* and *TAF15*, and the sequence mutations of *ZEB2*, *CREBBP*, and *SETD1B*, are found in both *ZNF384-r* and *ZNF362-r* BCP-ALL. The zinc finger domains are retained in both fusion proteins [8].

The Ph-like subtype can successfully exemplify significant improvements in prognosis by seeking the phenocopied events. However, extra effort is required to identify other possible phenocopied subtypes (e.g., *HLF* fusion-like and hypodiploid-like subtypes) [8]. Moreover, the natural history and cell-of-origin of these “like” or “phenocopy” subtypes are still largely elusive. These gaps may prevent researchers from understanding the potential prognostic factors. A comprehensive comparison of the subtypes sharing similar gene expression profiles in many other aspects, such as cancer cell population, inherited or *de novo* variants within a noncoding region, aberrant splicing, bacterial and viral infections, chromatin accessibility, and/or epigenetics alterations, may provide more hints [27,87,94–105].

PAX5-driven subtypes: PAX5alt and PAX5 p.Pro80Arg

Paired box 5 (*PAX5*) is a member of the paired box (*PAX*) family and is an early B-lineage-specific transcriptional activator protein. Genetic alterations of *PAX5*, including DNA CNVs, sequence mutations, and chromosomal translocations, are common in patients with BCP-ALL

[106]. CNVs and non-silent sequence mutations of *PAX5* occur in about 30% and 5%–9% of all BCP-ALL patients [8,9,18]. Chromosomal translocations of *PAX5*, which result in fusion genes, account for approximately 5%–7% of children and 2%–4% of adults with BCP-ALL [8,107]. *PAX5* fusions are highly heterogeneous and complex. At least 24 partner genes (e.g., *PAX5-JAK2*, *PAX5-ETV6*, and *PAX5-NOL4L*) of *PAX5* fusions are involved in *PAX5* rearrangements, thereby resulting in the expression of chimeric in-frame fusion transcript [9]. Furthermore, 15%–25% of patients with *PAX5* fusions have presented Ph-like subtype characteristics, mainly those of *PAX5-JAK2* and *PAX5-ZCCHC7*. Nearly 20% of *PAX5* fusions coexist with other chromosomal alterations, including *CRLF2* fusions, *ETV6-RUNX1*, *TCF3-PBX1*, *KMT2A*, *BCR-ABL1*, and *iAMP21*. For instance, *CRLF2* fusions coexist in up to 10% of all *PAX5* fusions, such as *PAX5-NOL4L*, *PAX5-AUTS2*, *PAX5-NCOA5*, and *P2RY8-CRLF2* pairs. Notably, these fusions have shown different gene expression profiles compared with the *CRLF2* fusions clustered to the *BCR-ABL1*/Ph-like subtype and account for up to 20% of all *CRLF2* fusions [8,9].

In recent studies, two new subtypes (*PAX5*-driven) with specific *PAX5* alterations have been defined in BCP-ALL. The first subtype is *PAX5alt* with rearrangements, intragenic amplifications, or sequence mutations of *PAX5* [8,9]. The second subtype is the hotspot mutation *PAX5* p.Pro80Arg (P80R) and biallelic *PAX5* alterations [8,9,65,86]. *PAX5alt* and *PAX5* P80R occur in 7%–10% and 3%–4% of childhood and 4%–8% and 1% of adult patients with BCP-ALL. Moreover, both subtypes are associated with intermediate outcomes. Additionally, compared with adults with *PAX5alt*, adults with *PAX5* P80R had more superior outcomes [8,9].

Diverse *PAX5* alterations were found in approximately 75% of patients in the *PAX5alt* subtype. The alterations include *PAX5* rearrangements (*PAX5-ETV6*, *PAX5-NOL4L*, *PAX5-AUTS2*, *PAX5-CBFA2T3*, *PAX5-DACH1*, *PAX5-FOXP1*, and *PAX5-ZNF521*), sequence mutations (*PAX5* p.Pro32Ser (P32S), p.Pro34Leu (P34L), p.Arg38Cys (R38C)/p.Arg38His (R38H), and p.Arg140Leu (R140L)/p.Arg140Gln (R140Q)), and CNVs (mainly one copy loss and focal intragenic amplification of *PAX5*). The ratio of CNVs that is positive for *PAX5alt* showed lesser frequency than that of other subtypes, but focal intragenic amplification (8/10) of *PAX5* (*PAX5amp*) was observed [9]. Apart from *PAX5* alterations, other common genetic alterations in the *PAX5alt* subtype are the signaling molecules (e.g., *NRAS*, *KRAS*, and *FLT3*), cell-cycle regulator *CDKN2A* deletions, B-cell development (*IKZF1* and *VPREB1* deletions), transcriptional factors (*ZFP36L2* and *ETV6*), and epigenetics modifier (*KDM6A*). The gene expression data showed that cytokine receptor genes (e.g., *PDGFRB* and *FLT3*) are enriched in *PAX5alt*, which is in line with the activation mutations in signaling pathways [8,9].

Point mutations of PAX5 P80R in the DNA binding can affect the ability of PAX5 to bind DNAs and regulate expressions. These mutations represent the first molecular subtype defined on the basis of homogeneous hotspot mutations and gene expression profiles [8,9,65,86,108,109]. Most patients with PAX5 P80R presented distinct gene expression profiles and uniform genetic alterations. PAX5 P80R patients can promote the biallelic alteration of PAX5 *in vivo*, and this alteration frequently coexists with the hemizygous loss of PAX5. This scenario results in a higher mutation allele frequency compared with that of other PAX5 point mutations [9]. Hemizygous PAX5 P80R without the deletion of the wild-type PAX5 allele may present gene expression features in other subtypes, such as the Ph-like and PAX5alt. Activating mutations in signaling (Ras and JAK/STAT pathways), including *PTPN11* and *IL7R*, and inactivating mutations in epigenetic factor *SETD2* are the most common genetic alterations coexisting with PAX5 P80R [8,9,65,86].

PAX5-driven subtypes showed high heterogeneity in genetics, such as diverse patterning genes involved in PAX5 fusions, and sequence mutations scattered on the coding region of PAX5. This characteristic may further require diverse therapy agents, including a combination of chemotherapy and multi-inhibitors, and possibly immunotherapy. Additionally, different prognoses between adult and childhood PAX5alt indicates the presence of additional age-dependent factors that may affect the vitality, aggressiveness, and drug responsiveness of leukemic cells in this BCP-ALL subtype [9].

NUTM1 gene fusion

The NUT midline carcinoma family member 1 (*NUTM1*), also called nuclear protein in the testis, is located within chromosome 15q14. Previously, *NUTM1* fusions were mainly reported as translocations t(15;9)(q14;q34) and t(15;19)(q14;p13) that could result in *BRD3-NUTM1* and *BRD4-NUTM1* [110–113]. In recent years, rearrangements of *NUTM1* involving *ACIN1* (14q11), *CUX1* (7q22), *AFF1* (4q21), *BRD9* (5p15), *ZNF618* (9q32), *IKZF* (7p12), and *SLC12A6* (15q14) have been identified as a specific subtype (1%–2%) in BCP-ALL. This subtype is preliminarily considered a subtype of BCP-ALL associated with a favorable prognosis [8,9,16–18,114,115]. The *HOXA* gene family, particularly *HOXA9*, is upregulated in the *NUTM1-r* ALL, which has not been described in NUT midline carcinoma [8]. *KMT2A* fusions can regulate leukemogenic gene expressions, particularly the *HOXA* gene family, by modulating the acetylation of H3K27 and disturbing the telomeric silencing 1-like histone 3 lysine 79 (H3K79) methyltransferase DOT1L [51,116]. *HOXA9* can cooperate with the JAK/STAT signaling pathway and drive leukemia development [117]. The molecular mechanism of

NUTM1-r ALL is still largely unknown and thus needs further study. Both *NUTM1* and *KMT2A* fusions may drive leukemogenesis by disturbing epigenetic status and upregulating the *HOXA* gene family.

Other gene fusions and point mutations

Rearrangements of BCL2/MYC and/or BCL6

Translocations t(14;18)(q32;q21), t(8;14)(q24;q32), and t(3;14)(q27;q32) that result in *BCL2-IGH*, *MYC-IGH*, and/or *BCL6-IGH* fusions occur in approximately 2% of adults (mostly > 30 years old) with BCP-ALL and are less common in children. These translocations are associated with consistently poor responses in early treatment [9]. Low levels of circulating t(14;18)-positive cells can be found in approximately 50%–70% of healthy individuals but never develop into a disease [118–121]. Chromosomal alterations in *BCL2*, *MYC*, and/or *BCL6* have been frequently reported in chronic lymphocytic leukemia and double- or triple-hit lymphoma, which are rare in ALL with a B-cell-precursor immunophenotype [16,121–133]. The promoter regions of *BCL2*, *MYC*, and *BCL6* are usually affected by *IGH* translocations, causing an overexpression of the rearranged allele compared with the germline allele. This characteristic can dramatically activate the proliferation of leukemogenic blast cells [123]. At present, patients with the abovementioned alterations cannot be well cured because of the development of chemotherapy resistance [9,121]. This limitation poses a great challenge to patient treatment. The inhibition of cyclin-dependent kinase 7 (CDK7) has been reported as an optional target for reducing the resistance of BCL-2 in B-cell lymphoma models [133]. The developed therapeutic agents in B-cell lymphoma may also be effective in BCP-ALL. Additional functional assays and clinical tests are urgently needed to improve the survival rate in the *BCL2/MYC* and/or *BCL6-r* BCP-ALL.

ZEB2 p.His1038Arg (H1038R) and IGH-CEBPE gene fusion

Zinc finger E-box binding homeobox 2 (*ZEB2*), a member of the Zfh1 family of 2-handed zinc finger/homeodomain proteins, is a nuclear protein that can bind DNA and repress its transcriptional activity; this protein interacts with activated SMAD, a DNA binding protein, and recognizes an 8-bp palindromic sequence (GTCTAGAC) called the Smad binding element [134]. CCAAT enhancer binding protein epsilon (CEBPE) is a bZIP transcription factor that binds to certain DNA regulatory regions by means of homodimer formation. In a recent study, a hotspot mutation of *ZEB2* p.His1038Arg (H1038R) and

translocation t(14;14) (q11;q32), which results in *IGH-CEBPE* with a truncation of the 3' UTR, is defined as a rare subtype (< 1%) sharing similar gene expression features. The rs2239630 G > A at the promoter of *CEBPE* is associated with the *IGH-CEBPE* translocated ALL with increased *CEBPE* expression [135]. More than 50% of patients in this subtype also have *NRAS* sequence mutations. The leukemic oncogene *LMO1* is significantly upregulated in this subtype and is an important component of a transcriptional complex that includes TAL1, TCF12/HEB, TCF3/E2A, MYB, RUNX1, GATA3, and LDB1. This transcription complex can form a positive interconnected autoregulatory circuit that impacts the transformation in approximately 60% of patients with T-cell ALL (T-ALL) [77,136]. In addition, *SMAD1* and *BMP2* are significantly downregulated in this subtype; these genes can regulate the signals of the bone morphogenetic proteins and are involved in a range of biological activities, including morphogenesis, cell growth, apoptosis, development, and immune responses [137–140]. Preliminarily, *ZEB2* mutation is associated with poor event-free survival and high relapse in patients with BCP-ALL [141]. The clinical implications of *ZEB2* p.His1038Arg (H1038R) and *IGH-CEBPE* gene fusion subtype are still largely unclear. Much larger sample sizes and functional tests are needed for this BCP-ALL subtype.

IKZF1 p.Asn159Tyr (N159Y)

IKZF1, also known as IKAROS, is a critical transcription factor related to the differentiation and maturation of the B-cell precursor. Somatic alterations of *IKZF1* are a hallmark of high-risk BCP-ALL with poor response to therapy [72,109,142]. Point mutations of *IKZF1* p.Asn159Tyr

(N159Y) were recently recognized as a rare subtype (< 1%) in BCP-ALL. In light of the limitation of sample size, the outcomes of *IKZF1* N159Y are still undermined. *IKZF1* N159Y, which is located in the DNA binding domain, may impact its capability for DNA binding and gene transcription regulation. Sequence mutations of *KRAS* are recurrent in patients with *IKZF1* N159Y but lack extra copy number alterations. The gene expression data showed that the transcriptional coactivator *YAP1* is significantly upregulated, which can drive *KRAS*-induced transformation through rescued cell viability in *KRAS*-dependent cells [143]. The chromatin remodeling *SALL1* and the signaling factor *ARHGEF28* are also significantly upregulated in *IKZF1* N159Y-positive patients. Meanwhile, the B-cell receptor signaling and JAK-STAT signaling pathways (e.g., *FLT3*, *FLT4*, and *STAT5*) are down-regulated in patients with *IKZF1* N159Y. These two pathways are commonly activated in other BCP-ALLs [8,9,144–146]. At present, the public data show that *IKZF1* N159Y-positive cases are still below 10. One case of *IKZF1* N159T was reported in the chronic myelomonocytic leukemia cohort [147]. Surprisingly, *de novo* germline mutations, including *IKZF1* N159S ($n = 6$) and *IKZF1* N159T ($n = 1$), could exist at the same *IKZF1* amino acid N159, which then would cause T-, B-, and myeloid cell-combined immunodeficiency, and a patient would develop T-ALL [148]. *Pneumocystis jirovecii* pneumonia is positive in all of patients with N159S or N159T mutations. A patient died at 2 years old without leukemia phenotype although the child received hematopoietic stem cell transplants [148]. Multi-center collaboration may accelerate the collection of patient data in this subtype for the further evaluation of its clinical significance (Table 1; Fig. 1A and 1B).

Table 1 Overview of biological subtypes of adult and childhood BCP-ALL

Subtype	Adult	Childhood	Key features	Molecular targeting agents	Outcomes
Ph	15%–25%	2%–5%	Gene fusion of <i>BCR-ABL1</i> (Ph), mutation of <i>RUNX1</i> , and common deletions of <i>PAX5</i> , <i>IKZF1</i> , and <i>CDKN2A/2B</i>	TKI; JAK/STAT, BTK/BCR, PD-1/PD-L1, CDK8, Aurora kinase A/B/C inhibitors	Poor outcome and improved with TKI
Ph-like	20%–25%	6%–15%	Gene fusions of <i>CRLF2</i> , <i>ABL1/ABL2</i> , <i>JAK2</i> , <i>EPOR</i> , <i>PDGFRB</i> , and <i>CSF1R</i> and mutations of <i>NRAS</i> , <i>KRAS</i> , <i>JAK2</i> , and <i>PTPN11</i>	TKI; JAK/STAT, BCL2 inhibitors	Poor outcome and amenable to TKI therapy
<i>KMT2A</i>	4%–10%	3%–4%	Gene fusions of <i>KMT2A</i> fused to <i>AFF1</i> , <i>MLLT1</i> , <i>MLLT3</i> , <i>MLLT10</i> , and <i>EP35</i> and mutations of <i>NRAS</i> , <i>KRAS</i> , and <i>FLT3</i> ; de-regulated gene expression of <i>HOXA</i> gene family, particularly <i>HOXA9</i>	DOT1L, HDAC, CDK4/6, BCL2, MEN1 inhibitors	Poor outcome
<i>KMT2A</i> -like	<1%	<1%	Gene fusions of <i>MED12-HOXA9</i> and <i>AFF1-TMEM156</i>	/	Poor outcome
<i>ETV6-RUNX1</i>	<1%	15%–25%	Gene fusion of <i>ETV6-RUNX1</i> and mutations of <i>WHSC1</i> , <i>KRAS</i> , and <i>NRAS</i>	/	Favorable outcome

(Continued)

Subtype	Adult	Childhood	Key features	Molecular targeting agents	Outcomes
<i>ETV6-RUNX1</i> -like	<1%	2%–3%	Co-existing <i>ETV6</i> and <i>IKZF1</i> aberrations; CD27 positive, CD44 low to negative	/	Intermediate outcome
<i>TCF3-PBX1</i>	2%–5%	4%–7%	Gene fusion of <i>TCF3-PBX1</i> and mutations of <i>TP53</i>	CDK4/6 inhibitors	Intermediate outcome with intensive therapy, and association with CNS relapse
<i>HLF</i>	<1%	<1%	Gene fusions of <i>TCF3-HLF</i> and <i>TCF4-HLF</i>	CDK4/6, TKI, BCL2, BCR/BCL6 inhibitors	Poor outcome
<i>DUX4</i>	4%–7%	4%–7%	Gene fusions of <i>IGH-DUX4</i> and <i>ERG-DUX4</i> ; de-regulated gene expression of <i>ERG</i> ; CD2 and CD371 positive	/	Favorable outcome with <i>ERG</i> deletions; intermediate outcome without <i>ERG</i> deletions
<i>MEF2D</i>	2%–7%	2%–4%	Gene fusions of <i>MEF2D</i> fused to <i>BCL9</i> , <i>SS18</i> , <i>FOXJ2</i> , <i>CSF1R</i> , <i>DAZAP1</i> , <i>STAT6</i> , <i>HNRNPUL1</i> , <i>HNRNPH1</i> , and <i>HNRNPM</i> ; de-regulated gene expression of <i>HDAC9</i> ; CD10 negative and CD38 positive	HDAC inhibitors	Poor outcome
<i>ZNF384</i>	3%–8%	3%–5%	Gene fusions of <i>ZNF384</i> fused to <i>EP300</i> , <i>TCF3</i> , <i>TAF15</i> , <i>CREBBP</i> , <i>EWSR1</i> , <i>ARID1B</i> , <i>SMARCA2</i> , <i>SMARCA4</i> , <i>SYNRG</i> , and <i>NIPBL</i> and mutations of <i>NRAS</i> , <i>KRAS</i> , <i>FLT3</i> , <i>PTPN11</i> , <i>SETD1B</i> , <i>ZEB2</i> , <i>EZH2</i> , <i>KMT2D</i> , and <i>CREBBP</i> ; mixed-phenotype	FLT3 inhibitors	Intermediate outcome
<i>ZNF384</i> -like	<1%	<1%	Gene fusions of <i>ZNF362</i> fused to <i>SMARCA2</i> and <i>TAF15</i>	/	/
<i>PAX5</i> alt	4%–8%	8%–10%	Gene fusions of <i>PAX5</i> fused to <i>ETV6</i> , <i>NOL4L</i> , <i>FOXP1</i> , <i>AUTS2</i> , <i>CBFA2T2/3</i> , <i>P2RY8-CRLF2</i> , deletions of <i>PAX5</i> , and mutations of <i>PAX5</i> , <i>NRAS</i> , <i>KRAS</i> , <i>FLT3</i> , and <i>JAK1</i>	TKI	Intermediate outcome
<i>BCL/MYC</i>	1%–2%	<1%	Gene fusions of <i>IGH-BCL2</i> , <i>IGH-MYC</i> , and <i>IGH-BCL6</i>	CDK7 inhibitors; BCL2 inhibitors	Poor outcome
<i>NUTM1</i>	<1%	1%–2%	Gene fusions of <i>NUTM1</i> fused to <i>ACIN1</i> , <i>CUX1</i> , <i>AFF1</i> , <i>BRD9</i> , <i>ZNF618</i> , <i>SLC12A6</i> , and <i>IKZF1</i>	Bromodomain inhibitors	Favorable outcome
High hyperdiploidy	<1%	15%–25%	>50 chromosomes, mutations of <i>NRAS</i> , <i>KRAS</i> , <i>FLT3</i> , <i>PTPN1</i> , <i>KMT2D</i> , and <i>CREBBP</i>	/	Favorable outcome
Near-haploid	<1%	2%–3%	25–29 chromosomes, mutations of <i>NRAS</i> , <i>FLT3</i> , and <i>PAX5</i> , and inactivation of <i>IKZF3</i> and <i>PAG1</i>	BCL2 inhibitors	Poor outcome
Low hypodiploid	1%–2%	10%–15%	32–39 chromosomes, mutations of <i>TP53</i> , deletions of <i>CDKN2A/2B</i> and <i>RB2</i> , and inactivation of <i>IKZF2</i>	BCL2 inhibitors	Poor outcome
High hypodiploid	<1%	<1%	40–43 chromosomes	/	Poor outcome
iAMP21	<1%	2%–3%	Complex structural alterations of chromosome 21	/	Intermediate outcome

(Continued)

Subtype	Adult	Childhood	Key features	Molecular targeting agents	Outcomes
PAX5 P80R	3%–4%	<1%	Hotspot mutations of <i>PAX5</i> p.Pro80Arg (P80R) and activating-mutations of <i>NRAS</i> , <i>KRAS</i> , <i>FLT3</i> , and <i>PTPN11</i>	TKI	Intermediate outcome
IKZF1 N159Y	<1%	<1%	Hotspot mutations of <i>IKZF1</i> p.Asn159Tyr (N159Y)	/	/
ZEB2 H1038R/ <i>IGH-CEBPE</i>	<1%	<1%	Gene fusion of <i>IGH-CEBPE</i> and mutations of <i>ZEB2</i> p.His1038Arg (H1038R), <i>NRAS</i> , <i>KMT2D</i> , <i>KRAS</i> , <i>KMT2A</i> , and <i>CDKN2A</i>	/	/

Percentages may not add up to 100% because of rounding. NA, not available. Abbreviations: TKI, tyrosine kinase inhibitor.

Diagnosis and molecular classification of BCP-ALL based on RNA-seq

Genetic variations with clinical significance in BCP-ALL are structurally heterogeneous [18]. Multiple high-throughput sequencing approaches are highly recommended, as they can be utilized to accurately recognize the prognostic factors (e.g., fusion genes, gene expression-dependent subtypes, small sequence variants, and genomic duplications and deletions) and determine the strategic therapy [149]. RNA-seq is a single and comprehensive platform for BCP-ALL diagnosis and genomic classification in the laboratory and clinical settings [9,43,150–152]. For example, most of the known fusion genes (e.g., *BCR-ABL1*, *ETV6-RUNX1*, and *TCF3-PBX1*) and new fusion genes (e.g., *TCF3/4-HLF*, *NUTM1*, *DUX4*, *ZNF384/ZNF362*, and *MEF2D* fusions) in BCP-ALL can be detected by RNA-seq [149,153]. These newly identified recurrent *DUX4*, *ZNF384*, *MEF2D*, and *NUTM1* fusions have distinct clinical features [8,9,15,16,18,22,64]. Notably, RNA-seq is also a reliable technology for simultaneously identifying the positive-fusion gene and the gene expression-dependent subtypes, including Ph-like, *ETV6-RUNX1*-like, *ZNF384*-like, and *KMT2A*-like. Small sequence variants and genomic deletions (e.g., *IKZF1*) are also detectable by RNA-seq in BCP-ALL [8,9,77,149,151–154]. For instance, by re-analyzing the RNA-seq data from different BCP-ALL cohorts, the molecular subtypes characterized by hotspot mutations (e.g., PAX5 P80R and ZEB2 H1038R) could be identified [8]. Exon-level genomic deletions can cause differential transcripts expression (e.g., *IKZF1* exons 4–7, 2–7, 2–8, and 4–8) and thus can be used to predict genomic deletion events [153]. RNA-seq was also applied in AML diagnosis to accurately detect small sequence variants, *FLT3*-internal tandem duplication (ITD), and *KMT2A*-partial tandem duplication (PTD) events [155–157].

However, RNA-seq is more susceptible to bias factors originating from the samples, technology platform, and

bioinformatics methodology (e.g., batch effect) compared with the DNA-based methods. Additional systematic benchmarks and further refinement of the methodology as a means of reducing the bias are needed to improve the stability and reducibility of the RNA-based methods [149,158,159].

New therapeutic targets and agents in BCP-ALL

Intensive chemotherapy and allogeneic hematopoietic cell transplantation were the core options of BCP-ALL treatment in the past [27]. Treatment toxicity with relapsed events induced by chemotherapy drugs has been one of the most critical concerns awaiting further resolution in BCP-ALL [13,27]. The advent of emerging inhibitors/antagonists and immunotherapeutic has launched a new era of target therapy in several molecular subtypes or unselected BCP-ALL patients (Table 2). This ongoing transformation may continuously reduce the use of chemotherapy drugs and consequently achieve less treatment-induced resistance events [160]. Molecular target therapy and cellular immunotherapy in BCP-ALL are mainly dependent on the specific genetics and gene expression markers of the patients’ leukemic cells in various molecular subtypes (e.g., *BCR-ABL1*, Ph-like, and *KMT2A* fusions) or the shared or unselected cell surface marker (e.g., CD19 and CD22) (Fig. 2). Several molecular subtypes in BCP-ALL, including R/R subtypes, have benefited from the new therapeutic targets and agents, although a large number of biomarkers are still rarely used as therapy targets.

BCR-ABL1 and Ph-like (e.g., *BCR-ABL1*-negative with fusions or mutations involved in *ABL1/ABL2*, *PDGFRA/B*, *EPOR*, and *CSF1R*) have benefited from TKIs, including imatinib and/or dasatinib [91]. The combination of dasatinib and c-JUN N-terminal kinase (JNK) inhibitor, i.e., JNK-IN-8, can significantly improve the survival of the *BCR-ABL1*-positive mice model [161]. The cyclin-dependent kinases 8 (CDK8) inhibitor, YKL-06-101,

Fig. 1 Estimated percentage of major molecular subtypes and the genomic landscape of genetic mutations. (A) Pie plot represents the percentage of molecular subtypes in adult and children patients with BCP-ALL. (B) Cycle plot indicates the genomic landscape of major genetic alterations, including gene fusions, sequence mutations, and DNA CNVs. Chromosomes are separately arranged from chromosome 1 to X. Gene fusions are linked by ribbons, and the fusions involving *ETV6-RUNX1*, *BCR-ABL1*, *TCF3-PBX1*, *TCF3/4-HLF*, *IGH*, *KMT2A*, *MEF2D*, *ZNF384*, *NUTM1*, and *PAX5* are highlighted. Genes affected by sequence mutations and DNA CNVs are listed at the external lines according to chromosome location. * Genes affected by different types of variations, i.e., fusion genes, CNVs, and sequence mutations.

Table 2 Summary of known and potential therapy targets in BCP-ALL

Therapy targets	Classification	Agents	PubMed ID	ClinicalTrials.gov identifier	Associated subtype
CD19	Immunotherapy	Blinatumumab; denintuzumab; SGN19a (denintuzumab mafodotin); SAR3419 (coltuximab ravtansine); AFM11; ADCT-42; KTE-C19 (autologous CD19 CAR T); CART-19 (autologous); UCART19 (allogeneic); C-CAR-011; iC9-CAR19 (autologous); CD19CAR-4-1BB-CD3zeta-EGFR-texpressing T lymphocytes (autologous); CART-19 (autologous); 4SCAR19 (autologous); CTL019 T-cells; CTL019 autologous T-cells (with tocilizumab); CD19CAT-41BBZ CAR T-cells (autologous); huCART19 (autologous); iC9/CAR.19/IL15-transduced CB-NK cells (umbilical and cord-blood derived); PCAR-019 (autologous); CD19 CAR-NK cells (allogeneic)	16352804, 20424114, 21849486, 22592608, 23307031, 24731302, 26041741, 26516065, 26907630, 27460500, 27846391, 27887660, 27571406, 28249141, 28202953, 28490811, 28698205, 28827408, 29385376, 30728140	NCT00450944, NCT01860937, NCT01864889, NCT01865617, NCT01974479, NCT01974479, NCT02003222, NCT02028455, NCT02030847, NCT02101853, NCT02143414, NCT02185781, NCT02228096, NCT02374333, NCT02412306, NCT02443831, NCT02454270, NCT02456350, NCT02458014, NCT02614066, NCT02669264, NCT02746952, NCT02772198, NCT02799550, NCT02807883, NCT02810223, NCT02819583, NCT02848911, NCT02851589, NCT02877303, NCT02879695, NCT02892695, NCT02906637, NCT02924753, NCT02935257, NCT02935543, NCT02968472, NCT02975687, NCT02997761, NCT03016377, NCT03018093, NCT03027739, NCT03056339, NCT03064269, NCT03076437, NCT03103971, NCT03109093, NCT03110640, NCT03114865, NCT03937544, NCT04012879	/
CD20	Immunotherapy	Rituximab; ofatumumab; REGN1979; CD20-CAR transduced T-cells (autologous)	18381448, 18780832, 18971949, 20628151, 21298738	NCT01363128, NCT02419469, NCT02651662, NCT01735604	/
CD22	Immunotherapy	Epratuzumab; inotuzumab; BL22 and moxetumomab pasudotox; CART22 cells (autologous)	21869836, 22128838, 23243285, 24579885, 25484043, 25552705, 25728039, 28152223, 28449314, 29155426, 31110217	NCT01371630, NCT01925131, NCT02311998, NCT02650414, NCT03094611, NCT03104491	/
CD19/CD20	Immunotherapy	CD19/20-CAR transduced T-cells (autologous or allogeneic)	28515942	NCT03097770	/
CD19/CD22	Immunotherapy	Combotox; deglycosylated ricin A chain conjugated CD19/CD22 immunotoxins; DT2219ARL	10803517, 12592332, 17706771, 19327829, 21732928, 29155426, 30581986, 31182121	NCT01408160, NCT03330691, NCT04094766	/
CD19/CD28	Immunotherapy	CAR T (autologous; CD19, CD28)	10048973, 20424114, 23515080, 28039295	NCT02146924	/
CD19/CD28/CD137	Immunotherapy	CD19 CAR/28 and CD19 CAR/28.137 T-cells (autologous)	27887866	NCT01853631, NCT02685670	/
CD19/CD133	Immunotherapy	Tandem CAR (TanCAR) of CD19 and CD133	30046161	/	/
CD19/CD137	Immunotherapy	Second generation CAR T (CD19, CD137)	27887866	NCT02965092	/
CD20/CD22	Immunotherapy	Hexavalent antibodies (HexAbs); Bs20x22	18025153, 20628151, 21347809	/	/
CD28/CD137	Immunotherapy	Third generation CAR T (CD28, CD137)	14961035, 27887866	NCT02186860	/
CD25	Immunotherapy	ADCT-301	25337274	NCT02588092	/
CD38	Immunotherapy	Isatuximab	26631114, 28483761, 30858549, 30862646	NCT03860844	/
CD52	Immunotherapy	Alentuzumab	28123068, 29264111	NCT00773149	/
CD123	Immunotherapy	XmAb14045	19454491, 27571406	NCT02730312	/
Integrin alpha4	Immunotherapy	Chemotherapy combined with natalizumab	23319569	/	/
ROR1	Immunotherapy	ROR1 CAR-specific T lymphocytes (autologous)	21813176, 29476010, 29849118, 30631148	NCT02706392	/
EPHA3	Immunotherapy	IIIA4	27922598	/	/

(Continued)					
Therapy targets	Classification	Agents	PubMed ID	ClinicalTrials.gov identifier	Associated subtype
PD-1/PD-L1	Inhibitors	Nivolumab; pembrolizumab; REG2810	/	NCT02651662, NCT02767934, NCT02819804	Ph
CTLA-4	Inhibitors	Ipilimumab	/	NCT00603772, NCT02879695	/
CDK4/6	Inhibitors	Palbociclib; ribociclib; PD0332991	17537993, 24736461, 25744718, 25813205, 26637365, 27099147, 29408328	NCT02310243, NCT03472573, NCT03515200, NCT03132454, NCT03792256	KMT2A, TCF3-PBX1, TCF3/4-HLF
CDK7	Inhibitors	THZ1	31085176	/	BCL/MLC
CDK8	Inhibitors	YKL-06-101	31628323	/	BCR-ABL1
Tyrosine kinase	Inhibitors	Dasatinib, PLX3397, nilotinib, sunitinib, sorafenib, ponatinib, ABL001 (asciminib)	17068151, 17077147, 19322212, 20807819, 22297722, 22897847, 23861246, 23974192, 24711557, 24464015, 24828076, 25049327, 25207766, 25759025, 26872634, 26773044, 27919910, 28329763, 28461505, 28408464, 28555080, 28819281, 29348129, 29681510, 29997224	NCT01620216, NCT02081378, NCT02390752, NCT02883049	Ph, Ph-like, HLF, PAX5alt, PAX5 P80R
BTK/BCR	Inhibitors	Ibrutinib	28031181	NCT02815059, NCT02997761, NCT02997761, NCT03267186, NCT03267186	Ph
FLT3, PI3K/mTOR pathway	Inhibitors	PKC412; idelalisib; sirolimus; quizartinib; crenolanib; dactolisib; rapamycin; CCI-779; TGR-1202	16195324, 17942929, 18704194, 22705992, 22955920, 27461063, 27784673, 28424165	NCT00651261, NCT00866281, NCT01162551, NCT01756118, NCT02779283, NCT03742323	ZNF384
JAK/STAT	Inhibitors	Ruxofitinib; AZD1480, CHZ868	20018760, 22955920, 25049327, 26175414, 26500062, 27860260, 28331226, 28369050, 28461505, 29907650	NCT01914484, NCT02420717, NCT02494882, NCT02723994	Ph
MEK1/2, RAS, B-Raf	Inhibitors	MEK162, trametinib, selumetinib; trametinib/sorafenib	27054332, 32220889	NCT02089230	/
SYK	Inhibitors	Entospletinib; PRT318; PRT260607	24948121, 26847027	NCT02404220	/
SRC	Inhibitors	/	24625531, 28804122	EudraCT number 2007-004070-18	/
Aurora kinase A/B/C	Inhibitors	Danuseritib	26073130, 28804122	/	Ph
PYST1 (Erk activation)	Inhibitors	BCI	/	/	/
JNK	Inhibitors	SP600125; JNK-IN-8	26310606, 26310606, 32552902	/	/
Casein Kinase II (CK2)	Inhibitors	CX-4945	32396934	/	/
VEGFR	Inhibitors	Axitinib	25686603	NCT02551718	/
LEPR	Inhibitors	1-day fasting	27941793	/	/
HSP90	Inhibitors	PU-H71	22271575, 26443624, 28619753	/	/
DRD2	Inhibitors	ONC201	29533922, 31127149	NCT02392572	/
MDM2	Inhibitors	DS302-b; RG7112; Nutlin-3	19421231, 19710698, 21986948, 29653964, 21986948	NCT02319369	/
MEN1	Inhibitors	VTP50469	31821784	/	KMT2A
HER2	Inhibitors	Trastuzumab	15531467, 18971949, 22267607	NCT00724360	/
PARP	Inhibitors	Talazoparib	24856976, 28634224	NCT02116777	/
Hedgehog	Inhibitors	PF-04449913	30487223, 31030089	NCT01841333	/

Therapy targets		Classification	Agents	PubMed ID	ClinicalTrials.gov identifier	(Continued)	Associated subtype
CXCR-4	Inhibitors	BL-8040; plerixafor (BKT140); LY2510924	AMD3100;	12835717, 24502926, 26031918, 26398122, 27071778, 27307990, 28409853, 28280274, 30254339, 19179467, 28171800, 29728108, 30841886	NCT01352650, NCT02605460, NCT02763384	/	/
DNA methyl-transferases (DNMT1/ DNMT3A/ DNMT3B)	Inhibitors	Decitabine; azacitidine; pinometostat			NCT00075010, NCT00349596, NCT01861002, NCT02141828, NCT02458235	/	/
Histone deacetylases (HDACs)	Inhibitors	Vorinostat; panobinostat; romidepsin; entinostat; chidamide; givinostat (ITF2357)		27428428, 27824051, 28331226, 30171027, 31439580, 31969338	NCT00217412, NCT00462605, NCT01132573, NCT01321346, NCT01422499, NCT02551718, NCT02553460, NCT03117751, NCT03564470, NCT03564704	MEF2D, KMT2A	
DOT1L	Inhibitors	EPZ-5676		23801631, 24993360, 28428443, 29724899	NCT01684150, NCT02141828, NCT03724084, NCT03701295	KMT2A	
c-Myc	Inhibitors	Shikonins, TGR-1202, JQ1		21949397, 21986948, 22904298, 27784673	/		
BCL2/BCL-X _L	Inhibitors	Venetoclax (ABT-199); ABT-737; navitoclax (ABT-263)		23788110, 26214592, 27054332, 28122742, 28974549, 30631148, 30862722	NCT03181126, NCT03236857, NCT03319901, NCT03504644, NCT03576547, NCT03808610, NCT03181126, NCT03826992, NCT04029688	KMT2A, Ph-like, HLF, BCL/MTc, near-haploid, low hypodiploid	
BCL-6	Inhibitors	PRT062607; RI-BPI		23107779, 26214592, 25759025, 25780007	/	/	/
Proteasome	Inhibitors	Ixazomib; bortezomib; carfilzomib; CX-4945		23357978, 26593250	NCT02228772, NCT02293109, NCT02535806, NCT02578511	/	/
BIRC5 (survivin)	Inhibitors	YM155		25895498, 30991025	/	/	/
Retinoid X receptor	Inhibitors	Bexarotene, carbacyclin, ATRA, 9- and 13-cis RA		26321221	/	/	/
Reactive oxygen species	Inhibitors	Verteporfin		26774450, 30563887, 31109083	/	/	/
Bromodomain	Inhibitors	BMS-986158		30723300	NCT03936465	NUTM1	
TP53	Agonist	SB225002		19710698, 23334668, 28600336, 28557976, 29300620, 30657737, 23644531, 25896649, 29365313, 29463563, 26980764	/	/	/
IL-15	Agonist	ALT-803		25977584, 28697888, 30514753	NCT01885897, NCT02890758	/	/
Fas	Agonist	Rimiducid (AP1903)			NCT03016377, NCT03056339	/	/

combined with the mTOR inhibitor can induce cell death of human *BCR-ABL1* leukemic cells [162]. Besides, both CDK4/6 inhibitors and Bcl-2 inhibitor are two types of molecular inhibitors that have been tested in R/R BCP-ALL [13,163], such as CDK4/6 inhibitors palbociclib (NCT02310243, NCT03472573, NCT03515200, NCT03132454, and NCT03792256) and Bcl-2 inhibitor venetoclax (NCT03826992, NCT03319901, NCT03181126, NCT04029688, NCT03808610, and NCT03504644). *KMT2A* fusions, *HLF* fusions, and other R/R BCP-ALL may benefit from the inhibition of the cell cycle and apoptosis pathways. De-regulated DNA methylation or histone deacetylation has been found in several BCP-ALL subtypes (e.g., *KMT2A* and *MEF2D* fusions). DOT1L inhibitors (e.g., pinometostat/EPZ-5676) have been tested in phase I trials (NCT01684150 and NCT02141828) for *KMT2A-r* leukemia [164], and the phase 1b/2 trials (NCT03724084 and NCT03701295) are currently recruiting patients. HDAC inhibitors (e.g., vorinostat and panobinostat) have also been proposed to be benefiting several BCP-ALL subtypes (NCT02553460), including *MEF2D* fusions and R/R BCP-ALL [16,18,64,165]. A newly proposed bioavailable Menin (*MEN1*)-*KMT2A* interaction inhibitor, VTP50469, showed that it can improve survival in patient-derived tumor xenograft mouse models of *KMT2A-r* BCP-ALL by suppressing a subset of *KMT2A* fusion target genes [166]. Other activated critical cellular pathways regulating cell proliferation and apoptosis (i.e., pre-B/B-cell receptor, RAS, JAK-STAT, and mTOR/PI3K) [13] are also promising targeted pathways. Numerous clinical trials have been registered. The test combining multiple molecular compounds or agents are still in progress. Nonetheless, additional work is required to verify whether the intensive dose of chemotherapy drugs can be reduced reasonably.

Apart from the inhibitors/antagonists, immunotherapeutic agents, such as CAR-T and monoclonal antibodies, are another promising strategy for targeting specific cell surface markers overexpressed in leukemic cells. Immunotherapeutic agents can be used in the therapy of most children and adults with R/R BCP-ALL. The cell membrane antigens CD19, CD20, and CD22 are the three most promising targets of immunotherapeutic agents for BCP-ALL [167–174]. Other bispecific agents (e.g., Combobox for CD19/CD22) are becoming the next-generation CAR-T treatment options. As one of the hottest fields in BCP-ALL, a series of clinical trials of CAR-T for R/R BCP-ALL is ongoing (e.g., NCT03330691, NCT03937544, NCT00450944, NCT04012879, and NCT04094766). The immunotherapeutic agents inotuzumab and blinatumomab were approved by the United States Food and Drug Authority for the therapy of adults with R/R BCP-ALL, which can help to improve in the future the overall survival of both children and adults with BCP-ALL. In addition, the combination of the TKIs

imatinib or dasatinib with multiagent chemotherapy is currently used in multiple clinical trials of R/R BCP-ALL. This treatment has markedly improved the outcome in BCP-ALL subset, as the five-year overall survival of patients has increased to 75% from less than 50% [12,175]. Controlling early death, reducing therapy-induced resistance mutations, and comprehensive clinical management of adult patients are the potential key issues of medical precision in BCP-ALL treatment (Table 2) [5,8,9,12,13,25,40,60,61,160,167,169,176–182].

Conclusions

Through decades of collaboration, more than 95% of patients with BCP-ALL have been classified and labeled using detectable genetic alterations, including distinct translocations of chromosomes, aneuploidy, DNA copy number alterations, sequence mutations, and gene expression patterns [8–12,183]. Refined risk stratification and the approval of new drugs and agents, including target inhibitors, monoclonal antibodies, and immunomodulators, and CAR-T, have resulted in an excellent five-year event-free survival and a five-year overall survival in children with BCP-ALL. However, the development of resistance and early death during treatments continue to pose daunting challenges for some subtypes of BCP-ALL, including hypodiploid (< 44 chromosomes), *HLF*-arranged, *BCL2/MYC-r*, *BCR-ABL1*/Ph-like, *KMT2A-r*, and *MEF2D-r* BCP-ALL. Additionally, single-cell-based traces of cancer cell populations, chromatin accessibility, epigenetic alterations, genome-wide germline mutations, functional non-coding and synonymous mutations, and other abnormalities at the non-genomic levels, such as protein and metabolic levels, are still poorly understood. Information on these aspects can help in drug discovery and improvement in the prognoses of leukemia patients, including BCP-ALLs [103–105,183–188]. Through the comprehensive identification of prognostic biomarkers and the development of new techniques in diagnosis and target treatment, we can further improve the survival time and life quality of patients with BCP-ALL.

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Compliance with ethical guidelines

Jianfeng Li, Yuting Dai, Liang Wu, Ming Zhang, Wen Ouyang, Jinyan Huang, and Saijuan Chen declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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