# Biological Markers of High-Risk Childhood Acute Lymphoblastic Leukemia

Contributor: Jiasen He, Faryal Munir, Samanta Catueno, Jeremy S. Connors, Amber Gibson, Lindsay Robusto, David McCall, Cesar Nunez , Michael Roth, Priti Tewari, Sofia Garces, Branko Cuglievan, Miriam B. Garcia

Childhood acute lymphoblastic leukemia (ALL) has seen significant advances in treatment, yet children classified as high-risk still face challenging outcomes. Traditionally, the severity of ALL was assessed using basic clinical information at diagnosis, but now a deeper understanding of specific biological markers—such as molecular profiles, genetic variations, and immune system characteristics—has become crucial. These markers are not just keys to understanding the disease's mechanisms, but also indicators of how it may progress and respond to treatment. For instance, the development of drugs like tyrosine kinase inhibitors can be used to target high-risk leukemia with certain genetic mutations. By focusing on the intricacies of high-risk childhood ALL, research is paving the way for more personalized and precise treatments, offering hope for better management of this complex disease.

## 1. High-Risk Molecular Genomic Subtypes

### 1.1. B-Lymphoblastic Leukemia/Lymphoma with BCR::ABL1 Fusion

The reciprocal translocation t(9;22) leads to the Philadelphia chromosome abnormality, which causes 2–5% of pediatric ALLs [1]. The Philadelphia chromosome, whose incidence increases as age advances, is the most common chromosomal abnormality in adult ALL, with an overall incidence of 20–25% [1][2][3][4]. Philadelphia chromosome-positive ALL (Ph+ ALL) is historically associated with worse outcomes, with long-term survival rates of 10–20% [4][5][6][7]. Before the availability of tyrosine kinase inhibitors (TKIs), hematopoietic stem cell transplantation (HSCT) provided a cure in only 50–60% of patients during the first remission [5][8][9].

The *BCR::ABL1* fusion oncoprotein that results from the reciprocal translocation t(9;22) has intrinsic tyrosine kinase activity [10][11][12]. *BCR::ABL1* fusion leads to the upregulation of several cell cycle signaling pathways, including RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, and JAK/STAT, and is associated with the activation of other tyrosine kinases such as SRC family members (e.g., LYN, HCK) and MYC [12][13][14]. The aberrant expression of the *BCR::ABL1* fusion oncoprotein in lymphohematopoietic cells results in dysregulated cell proliferation and reduced apoptosis through deregulated tyrosine kinase activity, making the protein an excellent molecular therapeutic target [15].

In chronic myeloid leukemia (CML), the BCR gene breakpoint typically occurs in the major breakpoint cluster region (M-BCR), leading to the production of a 210 kD BCR-ABL1 fusion protein (p210), whereas in Ph+ ALL, the breakpoint may be in either the M-BCR or the minor BCR (m-BCR), resulting in a 190 kD fusion protein (p190) [16][17]. The clinical presentation of CML in lymphoid blast crisis (BC) closely resembles Ph+ ALL, posing diagnostic challenges, particularly when M-BCR rearrangements are present and associated with the p210 protein, which is characteristic of CML [16][18]. This distinction is crucial for treatment decisions, as Ph+ ALL typically warrants chemotherapy combined with a tyrosine kinase inhibitor, while CML presenting in or progressing to BC often necessitates allogeneic stem cell transplantation, highlighting the importance of accurate leukemia subtyping for optimal therapeutic strategies [18].

The introduction of TKIs in the treatment of Ph+ ALL brought breakthrough improvements in outcomes and, hence, became part of standard-of-care frontline therapy. The COG AALL0031 study reported that the combination of the TKI imatinib with chemotherapy doubled the 5-year disease-free survival (DFS) rate of children with very high-risk Ph+ ALL to 70% [19]. A second-generation TKI, dasatinib, has a potency more than 300-fold that of imatinib and can permeate the blood–brain barrier, making it useful in the treatment of ALL patients with central nervous system disease; however, it does not completely prevent central nervous system relapse [20][21][22]. The COG AALL0622 study of patients with Ph+ ALL in which dasatinib was started on day 15 of induction therapy at a dose of 60 mg/m$^2$/day, showed that the treatment,

even in the absence of cranial irradiation, had results similar to those observed in COG AALL0031. COG AALL0622 also supported restricting HSCT to only slow responders [22]. A slightly higher dose of dasatinib (80 mg/m$^2$/day) was investigated by the Chinese Children's Cancer Group, who also found significant improvements in event-free survival (EFS) and OS, as well as fewer relapses compared with those who received imatinib [20][23].

An analysis of long-term follow up data from the EsPhALL2004 study, in which pediatric Ph+ ALL patients were treated with imatinib, yielded results similar to those observed in COG AALL0031 [19] and COG AALL0622 [22], thus emphasizing the need for early TKI exposure and de-emphasizing the need for HSCT in the future trials. This follow-up study also concluded that a WBC count of at least 100 × 10/L at the time of Ph+ ALL diagnosis predicted a worse prognosis [24].

The ideal TKI treatment duration has not been established conclusively; indeed, unless intolerable toxicity occurs, TKI treatment can last indefinitely [25][26][27]. In patients with Ph+ ALL, the ultimate goal of therapy is a sustained complete molecular response, which may be an independent prognostic factor for increased OS and may preclude the need for HSCT [4][28]. Additional studies to determine the duration are needed.

## 1.2. B-Lymphoblastic Leukemia/Lymphoma with BCR::ABL1-like Features

Philadelphia chromosome-like ALL (Ph-like ALL) is a recently discovered aggressive entity that shares genetic characteristics with Ph+ ALL, but lacks the BCR::ABL1 translocation abnormality [4][29][30]. Ph-like ALL is thrice as common as Ph+ ALL, representing about 10% of pediatric ALL, 15–25% of adolescent and young adult ALL, and 20–27% of adult ALL [31][32]. Among young adults of Hispanic descent, Ph-like ALL has a high prevalence (>50%) [31][33], which may be partially associated with the ethnic group's high rate of rearrangements of the cytokine receptor-like factor 2 gene *CRLF2* [31][34]. Ph-like ALL has adverse clinical traits and a dismal prognosis, with an estimated survival rate of less than 30% [31]. Furthermore, Ph-like ALL also has an increased association with Down syndrome [35][36].

Ph-like ALL has a complicated genomic landscape; the findings of genome and transcriptome sequencing studies suggest a variety of genetic changes that dysregulate various classes of cytokine receptors and tyrosine kinases [37]. Like those with Ph+ ALL, most patients with Ph-like ALL (70%) have hallmark *IKZF1* alterations [33][36][38][39], which are associated with high rates of induction therapy failure and a high risk of relapse [22][40].

It is worth noting that while the Ph-like gene expression signature holds diagnostic value, it has not yet been identified as a therapeutic target. For example, strategies for targeting therapy for *IKZF1* deletion are still not well-defined [35]. However, it is important to consider sentinel molecular lesions that are instrumental in driving leukemogenesis as potential targets. These alterations can be broadly categorized into major subclasses, such as ABL-class fusions, lesions that activate JAK/STAT signaling, and others that affect different signaling pathways.

The kinases altered in ABL-class fusions that phenocopy *BCR-ABL1* include platelet-derived growth factor receptor alpha (PDGFRA) and beta (PDGFRB), colony stimulating factor 1 receptor (CSF1R), and ABL1 and ABL2, which provide targets for ABL inhibitors [41]. TKIs have shown efficacy against Ph+ ALL, as well as Ph-like ALL and T-ALL with ABL1-class fusions [42][43][44][45]. The alteration of CRLF2, JAK2, and EPOR can activate JAK/STAT signaling; thus, JAK2 inhibitors can potentially be used in patients with these alterations [35]. More than half of patients with Ph-like ALL have *CRLF2* rearrangements, and of those with such rearrangements, 50% have concurrent activating mutations of Janus kinases (JAK1, JAK2, and JAK3) [4][38]. Other cytokine receptor alterations involve PI3K, mTOR, and the JAK/STAT pathways. Mutations in JAK2 and EPOR are present in about 7% and 5% of cases, respectively, and are associated with worse outcomes [31][36]. Additionally, 4–10% of Ph-like ALL have mutations in RAS pathway members, including *KRAS*, *NRAS*, *NF1*, *PTPN11*, and *CBL1* [36].

## 1.3. B-Lymphoblastic Leukemia/Lymphoma with *KMT2A* Rearrangement

The lysine methyltransferase 2A gene *KMT2A* (also known as *MLL*), located on chromosome 11q23, can be rearranged with different gene loci and can occur in acute leukemias of lymphoid or myeloid origin [46]. *KMT2A* gene rearrangements occur in 10–15% of adult patients with B-ALL, but only 5% of children and young adults with ALL [47]. They are also found in about 70% of infants with ALL and are believed to be acquired in utero [46]. In infant ALL, *KMT2A* gene rearrangements are linked to poor prognosis, particularly in infants diagnosed before the age of 6 months, present with a WBC count of at least 300 × 10$^9$/L, or have a poor response to induction therapy with steroids [48]. *KMT2A*-rearranged ALL is a high-risk subgroup with dismal treatment responses and a long-term survival rate of less than 60% [47][49]. Furthermore, therapy responses vary based on specific translocations. The Ponte-di-Legno Childhood ALL Working Group's recent retrospective study of 629 patients with 11q23/*KMT2A*-rearranged ALL reported a 5-year EFS rate of 69.1 ± 1.9% for the entire cohort, but a range of rates for patient subgroups. For instance, the 5-year EFS rate for patients with t(9;11)-positive

T-ALL (*n* = 9) was 41.7 ± 17.3%, whereas that for patients with t(4;11)-positive B-ALL (*n* = 266) was 64.8 ± 3.0% and that for patients with t(11;19)-positive T-ALL (*n* = 34) was 91.2 ± 4.9% [50].

Two international randomized studies of infant patients with *KMT2A*-rearranged ALL found no appreciable differences in outcomes between standard and intensified chemotherapy (the Interfant-99 study) or between myeloid- and lymphoid-type consolidation therapy (the Interfant-06 study) [51][52]. Recently, Stutterheim et al. looked at the clinical implications of MRD in infants with *KMT2A*-rearranged ALL treated on the Interfant-06 protocol. The study demonstrated an improved DFS based on stratification of therapy according to MRD at the end of induction. Infants with high MRD levels at the end of induction therapy benefited more from acute myeloid leukemia (AML)-like consolidation therapy (6-year DFS, 45.9%) than from ALL-like consolidation therapy (23.2%), whereas those with low MRD levels at the end of induction therapy may respond better to ALL-like consolidation regimens (6-year DFS, 78.2%) than to AML-like regimens (45.0%); patients with MRD at end of consolidation therapy continued to have grim outcomes. These results will pave the way for more treatment interventions in the next Interfant protocol [48].

## 2. High-Risk Cytogenetic Features

### 2.1. Hypodiploid ALL

Hypodiploid ALL, which is identified by the presence of less than 44 chromosomes or a DNA index (the ratio of the amount of DNA in a leukemia sample to the amount of DNA in normal peripheral blood mononuclear cells) of less than 0.81, can be subclassified as near-haploid ALL (24–31 chromosomes), low-hypodiploid ALL (32–39 chromosomes), or high-hypodiploid ALL (40–43 chromosomes). Hypodiploid ALL accounts for 1–2% of pediatric ALL. Hypodiploidy is a poor prognostic factor [20][53][54]. Patients with near-haploid ALL frequently have mutations involving the RAS and PI3K pathways and deletion of *IKZF3* [20][55]. By contrast, 90% of patients with low-hypodiploid ALL have leukemia cells with *TP53* mutations (about 50% of which are germline mutations) or somatic mutations in *IKZF2* and *RB1*. Hence, germline testing for *TP53* mutations (i.e., testing for Li–Fraumeni syndrome) is recommended for patients with low-hypodiploid ALL [20][56][57]. In some cases, hypodiploid clones are duplicated and appear to be pseudo-hyperdiploid clones; it is critical to confirm whether hypodiploid ALL is present to ensure that the correct risk stratification system is used and known risks associated with the disease are identified [20][58].

The preferred treatment modality for patients with hypodiploid ALL is historically HSCT, but is shifting towards molecular therapies. Two recent multicenter studies demonstrated that HSCT confers no benefit in patients with hypodiploid ALL, particularly those who have no MRD after remission-induction therapy, for whom the EFS rate was approximately 70% [20][53][54]. Patients in whom conventional chemotherapy fails to achieve remission can be considered for salvage treatment with BCL2 inhibitors, PI3K inhibitors, immunotherapy, or CAR T-cell therapy [20][55][59][60].

### 2.2. ALL with Intrachromosomal Amplification of Chromosome 21

ALL with intrachromosomal amplification of chromosome 21 (iAMP21) is a cytogenetic subset of pediatric ALL that was first described in 2003 [20][61][62][63]. It is characterized by the amplification of the *RUNX1* gene (≥5 copies per cell) and duplication of chromosome 21 detected with fluorescence in situ hybridization for the *ETV6::RUNX1* fusion gene [20]. iAMP21 seems to arise through multiple breakage–fusion bridge cycles. Patients with the germline Robertsonian translocation rob(15;21) or a germline ring chromosome 21 r(21) have an increased risk of B-ALL with iAMP21 [61][64]. ALL with iAMP21 is a rare but high-risk disease that accounts for 1–2% of pediatric ALL; it is seen more frequently in slightly older children (median age, 9 years) and is associated with lower WBC counts and a grim prognosis [61]. There have been rare instances of iAMP21 co-occurring with other recognized chromosomal abnormalities, such as high hyperdiploidy, *BCR::ABL1*, or *ETV6::RUNX1* [61][65][66]. Otherwise, iAMP21 is a primary cytogenetic abnormality that remains structurally consistent from initial diagnosis through relapse [67]. Similar chromosome 21 anomalies have been observed in myelodysplastic syndromes and AML, typically in conjunction with complicated karyotypes. In those instances, however, chromosomal regions other than that containing *RUNX1* seem to be involved [68][69]. Other cytogenetic abnormalities observed in ALL with iAMP21 ALL include the gain of chromosome X, the loss or deletion of chromosome 7, the deletion of *ETV6* or *RB1*, and the inactivation of *SH2B2* [20][65][70].

In patients with ALL with iAMP21, conventional standard-risk chemotherapy is associated with a poor response and higher relapse rates [71][72]. Intensive chemotherapy regimens offer only slightly better outcomes, with an EFS rate of about 70% [20]. Hence, trials of novel molecular therapies for ALL with iAMP21 are warranted.

# 3. High-Risk Immunophenotypes

## 3.1. Early T-Cell Precursor ALL

Early T-cell precursor ALL (ETP-ALL) was recently recognized as a subset of T-cell leukemias with increased molecular heterogeneity [4][20]. ETP-ALL accounts for 10–15% of T-ALL cases and is characterized by genetic features similar to those of hematopoietic stem cells and the early T-cell development immunophenotype (cytoplasmic CD3$^+$, CD1a$^-$, CD8$^-$, CD5$^{-/dim}$) and by some atypical myeloid antigen positivity [4][73]. Compared with T-ALL, ETP-ALL has a lower frequency of *NOTCH1* mutations and higher frequencies of *FLT3* and *DNMT3A* mutations [74][75][76][77]. ETP-ALL has several genomic features similar to those of T/myeloid MPAL, such as an increased incidence of biallelic WT1 changes and mutations in transcriptional regulators; epigenetic regulators; and signaling pathways, including JAK/STAT, RAS, PI3K/AKT/mTOR, FLT3, and MAPK [75][78][79]. Owing to increased glucocorticoid resistance, the disease has an innately poor response to conventional induction therapy, which contributes to a higher incidence of induction therapy failure and persistent MRD [4][73][74][77][80][81]. However, in the COG AALL0434 study, the long-term survival rate of ETP-ALL patients (91%), despite their high rate of MRD at the end of induction therapy, was similar to that of non-ETP-ALL patients (91.5%) [82]. Hence, until more data become available, the current recommendation is to treat ETP-ALL patients on the same protocol as non-ETP-ALL patients [83]. Further clinical trials are warranted to explore the genetic implications of ETP-ALL biology and optimal therapeutic targets.

## 3.2. Mixed-Phenotype Acute Leukemia

Mixed-phenotype acute leukemia (MPAL), which comprises a heterogenous group of uncommon hematological malignancies (not restricted to a single lineage) that express a combination of antigens, accounts for 2–5% of pediatric acute leukemias [79][84][85][86]. MPAL can switch lineages during treatment, which presents extreme diagnostic and therapeutic challenges, owing to a lack of consensus regarding treatment regimens [84][86].

In the 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia [87], MPAL is categorized as MPAL, B/myeloid, not otherwise specified (NOS); MPAL, T/myeloid, NOS; and MPAL, NOS, rare types (T/B/myeloid). The disease has two genomic categories: (1) MPAL with t(9;22) (q34.1;q11.2); BCR-ABL1 and (2) MPAL with t(v;11q23.3); KMT2A-rearranged [87][88][89].

*ZNF384* rearrangement occurs in 40–50% of pediatric B/myeloid MPAL, but is rare in adult MPAL [88][89]. B/myeloid MPAL with *ZNF384* rearrangement and *KMT2A* rearrangement displays enhanced FLT3-mediated signaling regardless of whether somatic FLT3 mutations are present [89]. One study reported that FLT3-ITD is a recurrent mutation in MPAL and suggested that the immunophenotype and, hence, leukemogenesis differs between B/myeloid and T/myeloid MPAL [90]. Biallelic WT1 alterations are more frequent in T/myeloid MPAL, which has some genomic features similar to those of ETP-ALL [79].

Multinational retrospective studies have shown that an ALL-based induction regimen is more efficacious than an AML-like or combined-type regimen in patients with MPAL [88][91]. However, treatment can be switched to an AML-like regimen if induction therapy with an ALL-like regimen fails. Although the role of HSCT in the treatment of MPAL is controversial, there is a growing inclination towards using the modality after the first complete remission [89].

---

## References

1. Foà, R.; Chiaretti, S. Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia. N. Engl. J. Med. 2022, 386, 2399–2411.

2. Ribeiro, R.C.; Abromowitch, M.; Raimondi, S.C.; Murphy, S.B.; Behm, F.; Williams, D.L. Clinical and biologic hallmarks of the Philadelphia chromosome in childhood acute lymphoblastic leukemia. Blood 1987, 70, 948–953.

3. Moorman, A.V.; Chilton, L.; Wilkinson, J.; Ensor, H.M.; Bown, N.; Proctor, S.J. A population-based cytogenetic study of adults with acute lymphoblastic leukemia. Blood 2010, 115, 206–214.

4. Samra, B.; Jabbour, E.; Ravandi, F.; Kantarjian, H.; Short, N.J. Evolving therapy of adult acute lymphoblastic leukemia: State-of-the-art treatment and future directions. J. Hematol. Oncol. 2020, 13, 70.

5. Chao, N.J.; Blume, K.G.; Forman, S.J.; Snyder, D.S. Long-term follow-up of allogeneic bone marrow recipients for Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 1995, 85, 3353–3354.

6. Pui, C.H.; Crist, W.M.; Look, A.T. Biology and clinical significance of cytogenetic abnormalities in childhood acute lymphoblastic leukemia. Blood 1990, 76, 1449–1463.

7. Thomas, X.; Thiebaut, A.; Olteanu, N.; Danaïla, C.; Charrin, C.; Archimbaud, E.; Fiere, D. Philadelphia chromosome positive adult acute lymphoblastic leukemia: Characteristics, prognostic factors and treatment outcome. Hematol. Cell Ther. 1998, 40, 119–128.

8. Aricò, M.; Schrappe, M.; Hunger, S.P.; Carroll, W.L.; Conter, V.; Galimberti, S.; Manabe, A.; Saha, V.; Baruchel, A.; Vettenranta, K.; et al. Clinical outcome of children with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia treated between 1995 and 2005. J. Clin. Oncol. 2010, 28, 4755–4761.

9. Schultz, K.R.; Prestidge, T.; Camitta, B. Philadelphia chromosome-positive acute lymphoblastic leukemia in children: New and emerging treatment options. Expert Rev. Hematol. 2010, 3, 731–742.

10. Nowell, P.C. The minute chromosome (Phl) in chronic granulocytic leukemia. Blut 1962, 8, 65–66.

11. Rowley, J.D. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature 1973, 243, 290–293.

12. Brown, V.I.; Seif, A.E.; Reid, G.S.; Teachey, D.T.; Grupp, S.A. Novel molecular and cellular therapeutic targets in acute lymphoblastic leukemia and lymphoproliferative disease. Immunol. Res. 2008, 42, 84–105.

13. Ilaria, R.L.; Van Etten, R.A. P210 and P190(BCR/ABL) induce the tyrosine phosphorylation and DNA binding activity of multiple specific STAT family members. J. Biol. Chem. 1996, 271, 31704–31710.

14. Skorski, T.; Bellacosa, A.; Nieborowska-Skorska, M.; Majewski, M.; Martinez, R.; Choi, J.K.; Trotta, R.; Wlodarski, P.; Perrotti, D.; Chan, T.O.; et al. Transformation of hematopoietic cells by BCR/ABL requires activation of a PI-3k/Akt-dependent pathway. EMBO J. 1997, 16, 6151–6161.

15. Skorski, T.; Nieborowska-Skorska, M.; Wlodarski, P.; Wasik, M.; Trotta, R.; Kanakaraj, P.; Salomoni, P.; Antonyak, M.; Martinez, R.; Majewski, M.; et al. The SH3 domain contributes to BCR/ABL-dependent leukemogenesis in vivo: Role in adhesion, invasion, and homing. Blood 1998, 91, 406–418.

16. Kelliher, M.; Knott, A.; Mclaughlin, J.; Witte, O.N.; Rosenberg, N. Differences in oncogenic potency but not target cell specificity distinguish the two forms of the BCR/ABL oncogene. Mol. Cell. Biol. 1991, 11, 4710–4716.

17. Suryanarayan, K.; Hunger, S.P.; Kohler, S.; Carroll, A.J.; Crist, W.; Link, M.P.; Cleary, M.L. Consistent involvement of the bcr gene by 9; 22 breakpoints in pediatric acute leukemias. Blood 1991, 77, 324–330.

18. Kolenova, A.; Maloney, K.W.; Hunger, S.P. Philadelphia Chromosome–positive Acute Lymphoblastic Leukemia or Chronic Myeloid Leukemia in Lymphoid Blast Crisis. J. Pediatr. Hematol./Oncol. 2016, 38, e193–e195.

19. Schultz, K.R.; Carroll, A.; Heerema, N.A.; Bowman, W.P.; Aledo, A.; Slayton, W.B.; Sather, H.; Devidas, M.; Zheng, H.W.; Davies, S.M.; et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia 2014, 28, 1467–1471.

20. Inaba, H.; Pui, C.H. Advances in the Diagnosis and Treatment of Pediatric Acute Lymphoblastic Leukemia. J. Clin. Med. 2021, 10, 1926.

21. Slayton, W.B.; Schultz, K.R.; Silverman, L.B.; Hunger, S.P. How we approach Philadelphia chromosome-positive acute lymphoblastic leukemia in children and young adults. Pediatr. Blood Cancer 2020, 67, e28543.

22. Slayton, W.B.; Schultz, K.R.; Kairalla, J.A.; Devidas, M.; Mi, X.; Pulsipher, M.A.; Chang, B.H.; Mullighan, C.; Iacobucci, I.; Silverman, L.B.; et al. Dasatinib Plus Intensive Chemotherapy in Children, Adolescents, and Young Adults With Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: Results of Children's Oncology Group Trial AALL0622. J. Clin. Oncol. 2018, 36, 2306–2314.

23. Shen, S.; Chen, X.; Cai, J.; Yu, J.; Gao, J.; Hu, S.; Zhai, X.; Liang, C.; Ju, X.; Jiang, H.; et al. Effect of Dasatinib vs Imatinib in the Treatment of Pediatric Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA Oncol. 2020, 6, 358–366.

24. Biondi, A.; Cario, G.; De Lorenzo, P.; Castor, A.; Conter, V.; Leoni, V.; Gandemer, V.; Pieters, R.; Stary, J.; Escherich, G.; et al. Long-term follow up of pediatric Philadelphia positive acute lymphoblastic leukemia treated with the EsPhALL2004 study: High white blood cell count at diagnosis is the strongest prognostic factor. Haematologica 2019, 104, e13–e16.

25. Carpenter, P.A.; Snyder, D.S.; Flowers, M.E.; Sanders, J.E.; Gooley, T.A.; Martin, P.J.; Appelbaum, F.R.; Radich, J.P. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. Blood 2007, 109, 2791–2793.

26. Giebel, S.; Czyz, A.; Ottmann, O.; Baron, F.; Brissot, E.; Ciceri, F.; Cornelissen, J.J.; Esteve, J.; Gorin, N.C.; Savani, B.; et al. Use of tyrosine kinase inhibitors to prevent relapse after allogeneic hematopoietic stem cell transplantation for

patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: A position statement of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Cancer 2016, 122, 2941–2951.

27. Samra, B.; Kantarjian, H.M.; Sasaki, K.; Alotaibi, A.S.; Konopleva, M.; O'Brien, S.; Ferrajoli, A.; Garris, R.; Nunez, C.A.; Kadia, T.M.; et al. Discontinuation of Maintenance Tyrosine Kinase Inhibitors in Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia outside of Transplant. Acta Haematol. 2021, 144, 285–292.

28. Short, N.J.; Jabbour, E.; Sasaki, K.; Patel, K.; O'Brien, S.M.; Cortes, J.E.; Garris, R.; Issa, G.C.; Garcia-Manero, G.; Luthra, R.; et al. Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2016, 128, 504–507.

29. Jain, N.; Roberts, K.G.; Jabbour, E.; Patel, K.; Eterovic, A.K.; Chen, K.; Zweidler-McKay, P.; Lu, X.; Fawcett, G.; Wang, S.A.; et al. Ph-like acute lymphoblastic leukemia: A high-risk subtype in adults. Blood 2017, 129, 572–581.

30. Den Boer, M.L.; van Slegtenhorst, M.; De Menezes, R.X.; Cheok, M.H.; Buijs-Gladdines, J.G.; Peters, S.T.; Van Zutven, L.J.; Beverloo, H.B.; Van der Spek, P.J.; Escherich, G.; et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: A genome-wide classification study. Lancet Oncol. 2009, 10, 125–134.

31. Tran, T.H.; Loh, M.L. Ph-like acute lymphoblastic leukemia. Hematol. Am. Soc. Hematol. Educ. Program. 2016, 2016, 561–566.

32. Cario, G.; Leoni, V.; Conter, V.; Baruchel, A.; Schrappe, M.; Biondi, A. BCR-ABL1-like acute lymphoblastic leukemia in childhood and targeted therapy. Haematologica 2020, 105, 2200–2204.

33. Mullighan, C.G.; Miller, C.B.; Radtke, I.; Phillips, L.A.; Dalton, J.; Ma, J.; White, D.; Hughes, T.P.; Le Beau, M.M.; Pui, C.H.; et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature 2008, 453, 110–114.

34. Harvey, R.C.; Mulligan, C.G.; Chen, I.M.; Wharton, W.; Mikhail, F.M.; Carroll, A.J.; Kang, H.; Liu, W.; Dobbin, K.K.; Smith, M.A.; et al. 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, 5312–5321.

35. Tasian, S.K.; Loh, M.L.; Hunger, S.P. Philadelphia chromosome-like acute lymphoblastic leukemia. Blood 2017, 130, 2064–2072.

36. Pui, C.H.; Roberts, K.G.; Yang, J.J.; Mullighan, C.G. Philadelphia Chromosome-like Acute Lymphoblastic Leukemia. Clin. Lymphoma Myeloma Leuk. 2017, 17, 464–470.

37. Roberts, K.G.; Mulligan, C.G. Genomics in acute lymphoblastic leukaemia: Insights and treatment implications. Nat. Rev. Clin. Oncol. 2015, 12, 344–357.

38. Roberts, K.G. The biology of Philadelphia chromosome-like ALL. Best Pract. Res. Clin. Haematol. 2017, 30, 212–221.

39. Roberts, K.G.; Gu, Z.; Payne-Turner, D.; McCastlain, K.; Harvey, R.C.; Chen, I.M.; Pei, D.; Iacobucci, I.; Valentine, M.; Pounds, S.B.; et al. High Frequency and Poor Outcome of Philadelphia Chromosome-Like Acute Lymphoblastic Leukemia in Adults. J. Clin. Oncol. 2017, 35, 394–401.

40. Stanulla, M.; Dagdan, E.; Zaliova, M.; Möricke, A.; Palmi, C.; Cazzaniga, G.; Eckert, C.; Kronnie, G.t.; Bourquin, J.-P.; Bornhauser, B.; et al. IKZF1plus Defines a New Minimal Residual Disease–Dependent Very-Poor Prognostic Profile in Pediatric B-Cell Precursor Acute Lymphoblastic Leukemia. J. Clin. Oncol. 2018, 36, 1240–1249.

41. Wells, J.; Jain, N.; Konopleva, M. Philadelphia chromosome-like acute lymphoblastic leukemia: Progress in a new cancer subtype. Clin. Adv. Hematol. Oncol. 2017, 15, 554–561.

42. Sievers, E.L.; Linenberger, M. Mylotarg: Antibody-targeted chemotherapy comes of age. Curr. Opin. Oncol. 2001, 13, 522–527.

43. Bhojwani, D.; Pui, C.H. Relapsed childhood acute lymphoblastic leukaemia. Lancet Oncol. 2013, 14, e205–e217.

44. 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, 123–131.

45. Kobayashi, K.; Miyagawa, N.; Mitsui, K.; Matsuoka, M.; Kojima, Y.; Takahashi, H.; Ootsubo, K.; Nagai, J.; Ueno, H.; Ishibashi, T.; et al. TKI dasatinib monotherapy for a patient with Ph-like ALL bearing ATF7IP/PDGFRB translocation. Pediatr. Blood Cancer 2015, 62, 1058–1060.

46. Brown, P.; Pieters, R.; Biondi, A. How I treat infant leukemia. Blood 2019, 133, 205–214.

47. Wen, J.; Zhou, M.; Shen, Y.; long, Y.; Guo, Y.; Song, L.; Xiao, J. Poor treatment responses were related to poor outcomes in pediatric B cell acute lymphoblastic leukemia with KMT2A rearrangements. BMC Cancer 2022, 22, 859.

48. Stutterheim, J.; van der Sluis, I.M.; de Lorenzo, P.; Alten, J.; Ancliffe, P.; Attarbaschi, A.; Brethon, B.; Biondi, A.; Campbell, M.; Cazzaniga, G.; et al. Clinical Implications of Minimal Residual Disease Detection in Infants With. J. Clin.

Oncol. 2021, 39, 652–662.

49. Forgione, M.O.; McClure, B.J.; Eadie, L.N.; Yeung, D.T.; White, D.L. KMT2A rearranged acute lymphoblastic leukaemia: Unravelling the genomic complexity and heterogeneity of this high-risk disease. Cancer Lett. 2020, 469, 410–418.

50. Attarbaschi, A.; Möricke, A.; Harrison, C.J.; Mann, G.; Baruchel, A.; De Moerloose, B.; Conter, V.; Devidas, M.; Elitzur, S.; Escherich, G.; et al. Outcomes of Childhood Noninfant Acute Lymphoblastic Leukemia With 11q23/KMT2A Rearrangements in a Modern Therapy Era: A Retrospective International Study. J. Clin. Oncol. 2023, 41, 1404–1422.

51. Pieters, R.; Lorenzo, P.D.; Ancliffe, P.; Aversa, L.A.; Brethon, B.; Biondi, A.; Campbell, M.; Escherich, G.; Ferster, A.; Gardner, R.A.; et al. Outcome of Infants Younger Than 1 Year With Acute Lymphoblastic Leukemia Treated With the Interfant-06 Protocol: Results From an International Phase III Randomized Study. J. Clin. Oncol. 2019, 37, 2246–2256.

52. Pieters, R.; Schrappe, M.; De Lorenzo, P.; Hann, I.; De Rossi, G.; Felice, M.; Hovi, L.; LeBlanc, T.; Szczepanski, T.; Ferster, A.; et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): An observational study and a multicentre randomised trial. Lancet 2007, 370, 240–250.

53. Pui, C.H.; Rebora, P.; Schrappe, M.; Attarbaschi, A.; Baruchel, A.; Basso, G.; Cavé, H.; Elitzur, S.; Koh, K.; Liu, H.C.; et al. Outcome of Children With Hypodiploid Acute Lymphoblastic Leukemia: A Retrospective Multinational Study. J. Clin. Oncol. 2019, 37, 770–779.

54. McNeer, J.L.; Devidas, M.; Dai, Y.; Carroll, A.J.; Heerema, N.A.; Gastier-Foster, J.M.; Kahwash, S.B.; Borowitz, M.J.; Wood, B.L.; Larsen, E.; et al. Hematopoietic Stem-Cell Transplantation Does Not Improve the Poor Outcome of Children With Hypodiploid Acute Lymphoblastic Leukemia: A Report From Children's Oncology Group. J. Clin. Oncol. 2019, 37, 780–789.

55. Holmfeldt, L.; Wei, L.; Diaz-Flores, E.; Walsh, M.; Zhang, J.; Ding, L.; Payne-Turner, D.; Churchman, M.; Andersson, A.; Chen, S.-C.; et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. Nat. Genet. 2013, 45, 242–252.

56. Bassan, R.; Bourquin, J.-P.; DeAngelo, D.J.; Chiaretti, S. New Approaches to the Management of Adult Acute Lymphoblastic Leukemia. J. Clin. Oncol. 2018, 36, 3504–3519.

57. Qian, M.; Cao, X.; Devidas, M.; Yang, W.; Cheng, C.; Dai, Y.; Carroll, A.; Heerema, N.A.; Zhang, H.; Moriyama, T.; et al. TP53 Germline Variations Influence the Predisposition and Prognosis of B-Cell Acute Lymphoblastic Leukemia in Children. J. Clin. Oncol. 2018, 36, 591–599.

58. Safavi, S.; Paulsson, K. Near-haploid and low-hypodiploid acute lymphoblastic leukemia: Two distinct subtypes with consistently poor prognosis. Blood 2017, 129, 420–423.

59. Diaz-Flores, E.; Comeaux, E.Q.; Kim, K.L.; Melnik, E.; Beckman, K.; Davis, K.L.; Wu, K.; Akutagawa, J.; Bridges, O.; Marino, R.; et al. Bcl-2 Is a Therapeutic Target for Hypodiploid B-Lineage Acute Lymphoblastic Leukemia. Cancer Res. 2019, 79, 2339–2351.

60. Talleur, A.C.; Maude, S.L. Evidence-Based Minireview: What is the role for HSCT or immunotherapy in pediatric hypodiploid B-cell acute lymphoblastic leukemia? Hematology 2020, 2020, 508–511.

61. Harrison, C.J. Blood Spotlight on iAMP21 acute lymphoblastic leukemia (ALL), a high-risk pediatric disease. Blood 2015, 125, 1383–1386.

62. Harewood, L.; Robinson, H.; Harris, R.; Al-Obaidi, M.J.; Jalali, G.R.; Martineau, M.; Moorman, A.V.; Sumption, N.; Richards, S.; Mitchell, C.; et al. Amplification of AML1 on a duplicated chromosome 21 in acute lymphoblastic leukemia: A study of 20 cases. Leukemia 2003, 17, 547–553.

63. Soulier, J.; Trakhtenbrot, L.; Najfeld, V.; Lipton, J.M.; Mathew, S.; Avet-Loiseau, H.; De Braekeleer, M.; Salem, S.; Baruchel, A.; Raimondi, S.C.; et al. Amplification of band q22 of chromosome 21, including AML1, in older children with acute lymphoblastic leukemia: An emerging molecular cytogenetic subgroup. Leukemia 2003, 17, 1679–1682.

64. Li, Y.; Schwab, C.; Ryan, S.L.; Papaemmanuil, E.; Robinson, H.M.; Jacobs, P.; Moorman, A.V.; Dyer, S.; Borrow, J.; Griffiths, M.; et al. Constitutional and somatic rearrangement of chromosome 21 in acute lymphoblastic leukaemia. Nature 2014, 508, 98–102.

65. Harrison, C.J.; Moorman, A.V.; Schwab, C.; Carroll, A.J.; Raetz, E.A.; Devidas, M.; Strehl, S.; Nebral, K.; Harbott, J.; Teigler-Schlegel, A.; et al. An international study of intrachromosomal amplification of chromosome 21 (iAMP21): Cytogenetic characterization and outcome. Leukemia 2014, 28, 1015–1021.

66. Haltrich, I.; Csóka, M.; Kovács, G.; Török, D.; Alpár, D.; Ottoffy, G.; Fekete, G. Six Cases of Rare Gene Amplifications and Multiple Copy of Fusion Gene in Childhood Acute Lymphoblastic Leukemia. Pathol. Oncol. Res. 2013, 19, 123–128.

67. Rand, V.; Parker, H.; Russell, L.J.; Schwab, C.; Ensor, H.; Irving, J.; Jones, L.; Masic, D.; Minto, L.; Morrison, H.; et al. Genomic characterization implicates iAMP21 as a likely primary genetic event in childhood B-cell precursor acute lymphoblastic leukemia. Blood 2011, 117, 6848–6855.

68. Baldus, C.D.; Liyanarachchi, S.; Mrózek, K.; Auer, H.; Tanner, S.M.; Guimond, M.; Ruppert, A.S.; Mohamed, N.; Davuluri, R.V.; Caligiuri, M.A.; et al. Acute myeloid leukemia with complex karyotypes and abnormal chromosome 21: Amplification discloses overexpression of APP, ETS2, and ERG genes. Proc. Natl. Acad. Sci. USA 2004, 101, 3915–3920.

69. Roumier, C.; Fenaux, P.; Lafage, M.; Imbert, M.; Eclache, V.; Preudhomme, C. New mechanisms of AML1 gene alteration in hematological malignancies. Leukemia 2003, 17, 9–16.

70. Sinclair, P.B.; Ryan, S.; Bashton, M.; Hollern, S.; Hanna, R.; Case, M.; Schwalbe, E.C.; Schwab, C.J.; Cranston, R.E.; Young, B.D.; et al. SH2B3 inactivation through CN-LOH 12q is uniquely associated with B-cell precursor ALL with iAMP21 or other chromosome 21 gain. Leukemia 2019, 33, 1881–1894.

71. Heerema, N.A.; Carroll, A.J.; Devidas, M.; Loh, M.L.; Borowitz, M.J.; Gastier-Foster, J.M.; Larsen, E.C.; Mattano, L.A., Jr.; Maloney, K.W.; Willman, C.L.; et al. Intrachromosomal Amplification of Chromosome 21 Is Associated With Inferior Outcomes in Children With Acute Lymphoblastic Leukemia Treated in Contemporary Standard-Risk Children's Oncology Group Studies: A Report From the Children's Oncology Group. J. Clin. Oncol. 2013, 31, 3397–3402.

72. Moorman, A.V.; Robinson, H.; Schwab, C.; Richards, S.M.; Hancock, J.; Mitchell, C.D.; Goulden, N.; Vora, A.; Harrison, C.J. 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, 3389–3396.

73. Coustan-Smith, E.; Mullighan, C.G.; Onciu, M.; Behm, F.G.; Raimondi, S.C.; Pei, D.; Cheng, C.; Su, X.; Rubnitz, J.E.; Basso, G.; et al. Early T-cell precursor leukaemia: A subtype of very high-risk acute lymphoblastic leukaemia. Lancet Oncol. 2009, 10, 147–156.

74. Jain, N.; Lamb, A.V.; O'Brien, S.; Ravandi, F.; Konopleva, M.; Jabbour, E.; Zuo, Z.; Jorgensen, J.; Lin, P.; Pierce, S.; et al. Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: A high-risk subtype. Blood 2016, 127, 1863–1869.

75. Zhang, J.; Ding, L.; Holmfeldt, L.; Wu, G.; Heatley, S.L.; Payne-Turner, D.; Easton, J.; Chen, X.; Wang, J.; Rusch, M.; et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature 2012, 481, 157–163.

76. Neumann, M.; Coskun, E.; Fransecky, L.; Mochmann, L.H.; Bartram, I.; Sartangi, N.F.; Heesch, S.; Gökbuget, N.; Schwartz, S.; Brandts, C.; et al. FLT3 mutations in early T-cell precursor ALL characterize a stem cell like leukemia and imply the clinical use of tyrosine kinase inhibitors. PLoS ONE 2013, 8, e53190.

77. Neumann, M.; Heesch, S.; Schlee, C.; Schwartz, S.; Gökbuget, N.; Hoelzer, D.; Konstandin, N.P.; Ksienzyk, B.; Vosberg, S.; Graf, A.; et al. Whole-exome sequencing in adult ETP-ALL reveals a high rate of DNMT3A mutations. Blood 2013, 121, 4749–4752.

78. Liu, Y.; Easton, J.; Shao, Y.; Maciaszek, J.; Wang, Z.; Wilkinson, M.R.; McCastlain, K.; Edmonson, M.; Pounds, S.B.; Shi, L.; et al. The genomic landscape of pediatric and young adult T-lineage acute lymphoblastic leukemia. Nat. Genet. 2017, 49, 1211–1218.

79. Alexander, T.B.; Gu, Z.; Iacobucci, I.; Dickerson, K.; Choi, J.K.; Xu, B.; Payne-Turner, D.; Yoshihara, H.; Loh, M.L.; Horan, J.; et al. The genetic basis and cell of origin of mixed phenotype acute leukaemia. Nature 2018, 562, 373–379.

80. Bond, J.; Graux, C.; Lhermitte, L.; Lara, D.; Cluzeau, T.; Leguay, T.; Cieslak, A.; Trinquand, A.; Pastoret, C.; Belhocine, M.; et al. Early Response-Based Therapy Stratification Improves Survival in Adult Early Thymic Precursor Acute Lymphoblastic Leukemia: A Group for Research on Adult Acute Lymphoblastic Leukemia Study. J. Clin. Oncol. 2017, 35, 2683–2691.

81. Conter, V.; Valsecchi, M.G.; Buldini, B.; Parasole, R.; Locatelli, F.; Colombini, A.; Rizzari, C.; Putti, M.C.; Barisone, E.; Lo Nigro, L.; et al. Early T-cell precursor acute lymphoblastic leukaemia in children treated in AIEOP centres with AIEOP-BFM protocols: A retrospective analysis. Lancet Haematol. 2016, 3, e80–e86.

82. Wood, B.L.; Winter, S.S.; Dunsmore, K.P.; Devidas, M.; Chen, S.; Asselin, B.; Esiashvili, N.; Loh, M.L.; Winick, N.J.; Carroll, W.L.; et al. T-Lymphoblastic Leukemia (T-ALL) Shows Excellent Outcome, Lack of Significance of the Early Thymic Precursor (ETP) Immunophenotype, and Validation of the Prognostic Value of End-Induction Minimal Residual Disease (MRD) in Children's Oncology Group (COG) Study AALL0434. Blood 2014, 124, 1.

83. Teachey, D.T.; O'Connor, D. How I treat newly diagnosed T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma in children. Blood 2020, 135, 159–166.

84. Batra, S.; Ross, A.J. Pediatric Mixed-Phenotype Acute Leukemia: What's New? Cancers 2021, 13, 4658.

85. Steensma, D.P. Oddballs: Acute Leukemias of Mixed Phenotype and Ambiguous Origin. Hematol./Oncol. Clin. N. Am. 2011, 25, 1235–1253.

86. Maruffi, M.; Sposto, R.; Oberley, M.J.; Kysh, L.; Orgel, E. Therapy for children and adults with mixed phenotype acute leukemia: A systematic review and meta-analysis. Leukemia 2018, 32, 1515–1528.

87. Arber, D.A.; Orazi, A.; Hasserjian, R.; Thiele, J.; Borowitz, M.J.; Le Beau, M.M.; Bloomfield, C.D.; Cazzola, M.; Vardiman, J.W. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016, 127, 2391–2405.

88. Inaba, H.; Mullighan, C.G. Pediatric acute lymphoblastic leukemia. Haematologica 2020, 105, 2524–2539.

89. George, B.S.; Yohannan, B.; Gonzalez, A.; Rios, A. Mixed-Phenotype Acute Leukemia: Clinical Diagnosis and Therapeutic Strategies. Biomedicines 2022, 10, 1974.

90. Quesada, A.E.; Hu, Z.; Routbort, M.J.; Patel, K.P.; Luthra, R.; Loghavi, S.; Zuo, Z.; Yin, C.C.; Kanagal-Shamanna, R.; Wang, S.A.; et al. Mixed phenotype acute leukemia contains heterogeneous genetic mutations by next-generation sequencing. Oncotarget 2018, 9, 8441.

91. Hrusak, O.; de Haas, V.; Stancikova, J.; Vakrmanova, B.; Janotova, I.; Mejstrikova, E.; Capek, V.; Trka, J.; Zaliova, M.; Luks, A.; et al. International cooperative study identifies treatment strategy in childhood ambiguous lineage leukemia. Blood 2018, 132, 264–276.