Acute lymphocytic leukaemia

Hagop Kantarjian, Ching-Hon Pui, Elias Jabbour

Lancet 2025; 406: 950–62

Published Online August 1, 2025 https://doi.org/10.1016/S0140-6736(25)00864-5

Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA (Prof H Kantarjian MD, Prof E Jabbour MD); **Departments of Oncology, Global Pediatric Medicine and Pathology, St. Jude Children's Research Hospital, Memphis, TN, USA** (Prof C-H Pui MD)

Correspondence to: Prof Hagop Kantarjian, Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA **hkantarjian@mdanderson.org**

Acute lymphocytic leukaemia (ALL) is a haematological malignancy of the lymphoid progenitor cells. Enhanced genetic analyses have led to the identification of over 23 subtypes of B-cell and 17 subtypes of T-cell ALL. In parallel, the development of highly sensitive measurable residual disease assays have refined disease monitoring and risk stratification. Breakthroughs in molecular therapeutics and immunotherapies have improved treatment efficacy while reducing toxicity, challenging the traditional notion of 2·5–3 years of intensive chemotherapy. Notable progress includes the use of more potent BCR::ABL1 tyrosine-kinase inhibitors, and antibodies targeting CD19 and CD22 leukaemia surface antigens, which have delivered unprecedented outcomes in *BCR::ABL1*-positive ALL. Historically, adults have had poorer outcomes than paediatric cases, largely due to the higher prevalence of adverse genetic subtypes and less favourable genetic subtypes. However, development of new therapies has improved overall survival in B-cell ALL to approximately 80–90%, even in adult and infant populations. Chimeric antigen receptor T-cell therapies have also transformed outcomes for children with refractory or relapsed ALL and are now being incorporated into the front-line treatment of adult ALL. These innovations hold the promise of increasing the cure rates while reducing reliance on intensive chemotherapy and allogeneic stem-cell transplantation.

Introduction

Acute lymphocytic leukaemia (ALL) is a cancer caused by clonal proliferation of lymphoid progenitor cells in the bone marrow, often accompanied by extramedullary involvement.[1,2] The worldwide estimated incidence of ALL was greater than 150 000 in 2019 and the age-standardised incidence rate was estimated to have increased by 1·61 per year since 1990.[3] Genetic studies have identified inherited variants linked to ALL susceptibility, with frequencies varying by ethnicity, reflecting differences in ALL incidence.[4–6] ALL has a bimodal age distribution, peaking at around 5 and 50 years, with a median age of 14 years; 60% of patients are younger than age 20 years, 25% are age 20–60 years, and 11% are older than age 60 years at diagnosis.[1,7,8] Managing ALL is complex, requiring 2·5–3 years of intensive chemotherapy under expert care.[9]

In six decades, improvements in chemotherapy regimens using 10–15 chemotherapy agents across induction, consolidation, intensification, and maintenance phases, along with CNS prophylaxis have achieved cure rates of 80–90% in paediatric ALL at specialised centres. However, worldwide cure rates are closer to 60–70% due to the complexity of treatment, toxic effects, non-compliance, or abandonment of care. Outcomes often depend on financial resources and geography,[10] with higher cure rates among children of affluent families and in high-income countries. In adult ALL, similar regimens result in 5-year overall survival (OS) rates of approximately 60% for adults aged 20–39 years, 40% in patients aged 40–59 years, and less than 20–30% for those older than 60 years.[10,11] These disparities by age are partly due to the differences in the incidences of ALL subtypes with varied prognosis, and higher incidences of poor risk subtypes in adults compared with children. In addition, older patients (age ≥60 years) have lower tolerance to intensive chemotherapy, often necessitating dose reductions, omission of crucial drugs, or treatment discontinuations. Even within the same ALL subset (eg, Philadelphia chromosome [Ph]-positive ALL) or treatment strategies (eg, intensive chemotherapy, BCR::ABL1 tyrosine-kinase inhibitors [TKIs], immunotherapy, and chimeric antigen receptor [CAR] T-cell therapy), paediatric outcomes consistently surpass adult outcomes.

Major advances within the last decade were propelled by a greater understanding of disease pathophysiology, the ability to closely monitor measurable residual disease (MRD), and the introduction of novel therapies that target specific subsets of ALL.[9,12–14] Risk-adapted therapies are improving survival,[15,16] particularly with therapies targeting selective transcripts (eg, BCR::ABL1 TKIs)[17–20] or surface antigens (eg, CD19- and CD22-targeted antibodies), reducing the need for allogeneic haematopoietic stem-cell transplantation (HSCT), except for patients with high-risk disease.[12,13,21,22]

Search strategy and selection criteria

We searched MEDLINE (2010–24) and the American Society of Clinical Oncology and American Society of Haematology websites (2010–24). We used the search terms: "acute lymphoblastic or lymphocytic leukemia" or "ALL". We largely selected publications from the past 5 years but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for.

Clinical presentation

Signs and symptoms of ALL are non-specific and are related to bone marrow involvement, tumour burden, proliferation, and organ infiltration. Marrow can affect cytopenias leading to anaemia-related symptoms (eg, shortness of breath, fatigue, and oxygen insufficiency

affecting the heart, lungs, and brain), infections, and bleeding due to thrombocytopenia. The burden of leukaemia can cause constitutional symptoms, such as fever, weight loss, and night sweats, and spontaneous or treatment-associated tumour lysis, and chemical disseminated intravascular coagulopathy (occasionally clinical).[23] The most common symptoms include fatigue, fever, and easy bruising and bleeding. Unlike acute myeloid leukaemia, severe leukostasis is rare in ALL due to the smaller size and lower viscosity of lymphoblasts. Children can present with extremity and joint pains from leukaemic infiltration of the synovium or synovial fluid.[24]

Hepatosplenomegaly from ALL infiltration is noted in 20% of patients. Other extramedullary involvement includes the testes, skin, CNS, lungs, kidneys, or mediastinum (specifically in T-cell ALL).[25] Initial CNS involvement occurs in 5–8% of patients, and presents as cranial neuropathies and meningeal infiltration.[24,25] Chin numbness related to expansion of the marrow in the mandible, pressing on the inferior alveolar branch of the trigeminal nerve, is noted or elicited in 40–50% of patients with Burkitt-like ALL.[26]

Biology of ALL

Genomic analyses have identified over 23 subtypes of B-cell ALL and 17 subtypes of T-cell ALL.[5,27] These studies revealed the drivers and cooperative genomic alterations underlying these subtypes and have shown that many patients with ALL have germline genomic variations that influence leukaemia susceptibility and treatment response.[5,27,28] Genome-wide association studies of B-cell ALL have identified non-coding polymorphisms associated with ALL risk, often at loci encoding haematopoietic transcription factors and tumour suppressors.[29] These polymorphisms confer subtle but cumulative risk, with some influencing somatic mutations, germline *GATA3* alterations, and *CRLF2* rearrangements in *BCR::ABL1*-like ALL.[30] Pathogenic germline coding variants in genes, including *TP53*, *IKZF1*, *ETV6*, and *PAX5* are linked to rare familial cases and up to 4% of sporadic ALL cases.[28,29] Some variants are associated with specific subtypes, such as *TP53* in low-hypodiploid, and *ETV6* in high-hyperdiploid ALL.[28] Germline *IKZF1* variants are also linked to drug resistance.[5,29]

The biological and clinical characteristics of T-cell ALL subtypes are less well defined due to overall fewer cases. Pharmacotyping studies have shown that T-cell ALL drug sensitivity correlates with T-cell differentiation.[31] Immature subtypes, such as early T-precursor (ETP)-ALL and near ETP-ALL, exhibit high BCL2 activity and venetoclax sensitivity, whereas mature subtypes have higher BCL-XL and LCK activation, lower BCL2 activity, and dasatinib sensitivity.[31]

Diagnostic evaluation and prognostication

ALL is diagnosed by bone marrow evaluation, including morphological, immunophenotyping, and cytogenetic and molecular studies. A morphological diagnosis is defined by having more than 20% of marrow lymphoblasts.[32–34] Flow cytometric immunophenotyping is used to identify cell surface markers and consequently diagnose B-cell ALL, which makes up approximately 80% of cases, or T-cell ALL, accounting for the remaining 20%.

Precursor B lymphoblasts express CD19, CD22, CD79a, or PAX5, along with immature markers, such as TdT and CD34, but lack surface immunoglobulin.[33] Expression of cell surface markers, such as CD10 and CD20, varies depending on the maturity of the B lymphoblast. B-cell ALL can therefore be further categorised into precursor B-cell ALL or mature B-cell ALL. T lymphoblasts express CD3 (surface or cytoplasmic), CD5, CD7, and other T-lineage markers (eg, CD2, CD4, or CD8), and also TdT and CD34.[33] WHO classification recognises T-cell ALL, not otherwise specified ALL, and ETP-ALL. T-cell ALL includes several subtypes: thymic ($CD1a^+$), mature (surface $CD3^+$), early (both CD1a and surface CD3 negative), and the ETP-ALL subtype. ETP-ALL is characterised by absent or low CD5 expression, a lack of CD1a and CD8 expression, and positivity for myeloid (eg, CD11b, CD13, CD33, CD65, or CD117) or stem-cell markers. Recently identified novel ETP-like T-cell ALL cases account for 18% of T-cell ALL and are associated with worse outcomes.[27] Rarely, patients can present with a blast population that lacks differentiation of a single lineage, termed mixed phenotypic acute leukaemia, or acute leukaemia of ambiguous lineage.

B-cell ALL and T-cell ALL cases are also classified into various subtypes based on cytogenetic and molecular alterations to guide risk-adapted therapy. Conventional cytogenetics and fluorescence in situ hybridisation for the detection of genetic abnormalities, such as *BCR::ABL1*, should be performed to help with appropriate treatment selection and prognosis. Rearrangement between chromosomes 9 and 22 [t(9;22)] result in the formation of the Ph and *BCR::ABL1* oncogene. Most often, *BCR::ABL1* translocation results in the formation of the p190 or p210 oncoprotein depending on the location of the breakpoint in the *BCR* gene on chromosome 22. Identification of the specific oncoprotein can identify whether a patient has de novo Ph-positive B-cell ALL or chronic myeloid leukaemia in lymphoid blast crisis. Additional subtypes of B-cell ALL include several favourable subtypes: high-hyperdiploid (characterised by gains of specific chromosomes, particularly 4, 10, and 17), *ETV6::RUNX1* (commonly initiated in utero and rare in adults), *DUX4*-rearranged (despite poor initial response to remission induction with prednisone, vincristine, and asparaginase), and *NUTM1*-rearranged (notably in infants).[35,36] Unfavourable subtypes include low-hypodiploid ALL (linked to *TP53* alterations, including germline variants in half of paediatric cases), near-haploid, *PAX5*, *KMT2A*-rearranged (especially in infants younger than age

***Panel*: High-risk cytogenetic and molecular aberrations in B-cell acute lymphocytic leukaemia**

Genetic alterations

PAX5, *IZKF1*, *KMT2A*-rearranged, *IgH*-rearranged, *HLF*-rearranged, *ZNF384*-rearranged, *MEF2D*-rearranged, and *MYC*-rearranged

Cytogenetic alterations

Hypodiploidy (<44 chromosomes); complex karyotype (five or more chromosomal abnormalities); t[v;11q23] (eg, t[4;11] and others), t[11;19]; iAMP21; and t[17;19][q22;p13]

***BCR::ABL1*-like genomic alterations**

CRLF2; *JAK1*, *JAK2*, *JAK3*; *IL7R*; *TYK2*; *EPOR*; *NTRK*; *FLT3*; *LYN*; *PTK2B*; and *PDGFRα*, *PDGFRβ*, *FGFR*, *ABL1*, and *ABL2* rearrangements

12 months), and *BCR::ABL1*-like ALL (a genomically heterogeneous subtype) among others (panel).[35,36] *BCR::ABL1*-like ALL frequency increases with age, from 10–15% in childhood (age <18 years) ALL, to 20% in adolescents (16–20 years), 25–30% in young adults (21–39 years), and decreases to 10% in older adults (>60 years).[37,38] In the USA, *BCR::ABL1*-like ALL is more common in Hispanic patients and associated with *GATA3* polymorphism and increased risk of relapse.[38] Burkitt leukaemia (t[8;14]) is a rare subtype of B-cell ALL, characterised by *MYC* rearrangement, leading to constitutive *MYC* expression.[39]

Treatment for paediatric ALL

ALL is the most common childhood cancer and is characterised by remarkable outcomes in the paediatric population. Although no specific cause is known, genetic predispositions, such as Down syndrome, Li-Fraumeni syndrome, and ataxia telangiectasia, and inherited cancer-predisposing genes (eg, *PAX5*, *IKZF1*, or *ETV6*) are risk factors for developing ALL.[28] Conventional treatment for childhood ALL typically includes remission induction, consolidation, delayed intensification, CNS prophylaxis, and continuation therapy, spanning a total duration of 2·5–3 years.[36] Patients at low risk (ie, those with B-cell ALL, aged 1–10 years, white blood cells $<50\times10^9$/L, *ETV6::RUNX1* gene fusion, or high hyperdiploid with good MRD response during remission induction) are generally treated with a five-drug regimen, including a glucocorticoid, vincristine, asparaginase, mercaptopurine, and methotrexate. Patients at intermediate risk and high risk receive three additional drugs: an anthracycline, cyclophosphamide, and cytarabine.[36] The introduction of MRD-directed therapy has considerably improved outcomes, with 5-year OS rates surpassing 90% more than a decade ago.[40] However, the subsequent lack of new drug developments has led to intensified use of conventional treatments, which failed to yield further improvements, suggesting that the effectiveness of traditional approaches might have plateaued.[41] Studies have shown that omitting prophylactic cranial irradiation for all patients was feasible.[40] Using optimised intrathecal therapy during early remission induction and consolidation treatment successfully reduced the CNS relapse rate to less than 2%.[41]

Recently, new drugs have become available for paediatric ALL. *BCR::ABL1*-positive ALL was the first subtype to benefit from targeted treatment. Concordant with adult ALL, the addition of imatinib, a BCR::ABL1 TKI, significantly improved outcomes in this subgroup compared with traditional chemotherapy alone.[42] In a randomised trial, dasatinib showed superior CNS control and event-free survival (EFS) compared with imatinib.[18] The use of dasatinib has also substantially reduced the need for allogeneic HSCT.[18,43] Among the various subtypes of *BCR::ABL1*-like ALL, only those harbouring *ABL*-class fusions can be targeted with BCR::ABL1 TKIs.[44] Although several molecular therapeutics have shown promising early results in other subtypes of B-cell ALL, they have yet to advance to phase 3 clinical trials.[36]

Blinatumomab, the bispecific T-cell engager (BiTE) targeting CD3 and CD19, has shown remarkable efficacy in randomised trials involving children with relapsed B-cell ALL and in newly diagnosed standard risk B-cell ALL.[45–47] Two single-group trials reported promising results with the addition of one course of blinatumomab to standard or attenuated chemotherapy in infants with newly diagnosed *KMT2A*-rearranged ALL, achieving 2-year disease-free survival rates of 78–82%.[21,48] Inotuzumab ozogamicin has also shown excellent outcomes, with remission rates exceeding 50% in patients with relapsed or refractory B-cell ALL.[49,50] This response has enabled many patients to proceed to allogeneic HSCT. Ongoing studies aim to refine dosing regimens and schedules, in combination with ursodiol, to mitigate hepatotoxicity, particularly when administered close to transplantation.

CAR T-cell therapies targeting CD19 or dual CD19 and CD22 antigens have proven highly effective, even in patients who have been unresponsive to multiple previous treatments, including allogeneic HSCT.[51–54] These therapies achieve complete remission rates exceeding 90%, with most patients becoming MRD-negative. The 12-month EFS rates range from 50–70%. CAR T-cell therapy has shown effectiveness in treating extramedullary leukaemia, particularly testicular disease, sparing the need for local irradiation.[51,53] Research is now focused on advancing CAR T-cell technology to establish it as a definitive treatment, and on refining criteria to identify patients who might benefit from consolidative HSCT. As such, detectable MRD (sensitivity from 10^{-5} to 10^{-6} cells) by PCR or next-generation sequencing (NGS), with or without B-cell aplasia, has been identified as a strong predictor of relapse following CD19 CAR T-cell therapy.[55]

The development of precision treatments for T-cell ALL remains challenging. Dasatinib has shown efficacy in T-cell ALL with LCK involvement, as evidenced by findings from preclinical studies and case reports.[56,57] These findings have led to ongoing investigations of dasatinib for treating T-cell ALL. A promising study involving children and adults with relapsed or refractory T-cell ALL treated with a combination of venetoclax and navitoclax spurred the launch of a paediatric clinical trial (NCT05192889).[58] Venetoclax is also under investigation for patients with ETP-ALL (NCT06390319). Nelarabine has been associated with improved CNS control in T-cell ALL (Children's Oncology Group AALL0434 trial).[59] Daratumumab, a human immunoglobulin G kappa monoclonal antibody targeting CD38 with direct on-tumour and immunomodulatory mechanisms of action, was safely combined with chemotherapy and induced an overall response rate (at any timepoint) of 83·3% in children with relapsed or refractory T-cell ALL.[60] These findings show daratumumab's potential as an effective treatment option. Recently, fratricide-resistant CD7 CAR T cells have been developed and were successfully used to treat patients with relapsed or refractory T-cell ALL.[61,62]

Treatment of adult ALL

Treatment of adults with ALL has been revolutionised by the incorporation of targeted therapies, resulting in long-term OS rates of 80% in precursor B-cell ALL,[9,22] 80–90% in Ph-positive ALL,[14,20,63,64] and 60–70% in T-cell ALL (table 1).[59,78] Successful delivery of ALL treatment not only requires knowledge of the therapeutic regimens, but also proper management of anticipated toxic effects (table 2). Continuous treatment with BCR::ABL TKIs also requires toxicity management by both the haematologist and general provider.

Ph-positive ALL

Ph-positive ALL accounts for approximately 20–25% of ALL cases in adults and less than 5% of paediatric cases. The Ph-positive ALL incidence increases with age, comprising more than 50% of cases in patients aged 60 years and older.[14] Historically, Ph-positive ALL was considered a high-risk subtype until the introduction of the BCR::ABL1 TKIs in 2000. Combined with cytotoxic chemotherapy, Ph-positive ALL has become a highly curable disease from previously being highly fatal. Disease monitoring of *BCR::ABL1* transcripts with PCR testing and newer techniques including NGS is crucial for early identification of molecular relapse and identification of patients who could benefit from allogeneic HSCT.

Within the past two decades, various treatment strategies have been explored, including single-agent TKIs alone or with minimal chemotherapy (primarily in older patients), and TKI combinations with intensive chemotherapy and allogeneic HSCT in first complete remission. Among the six commercially available BCR::ABL1 TKIs, imatinib, dasatinib, and ponatinib were approved by the US Food and Drug Administration for the treatment of Ph-positive ALL and were also approved by the European Medicines Agency. All three TKIs exert their activity by binding to the ABL1 tyrosine kinase binding pocket of the BCR::ABL1 oncoprotein. Mutations in the ABL1 binding pocket can lead to resistance and consequent inactivity of the various BCR::ABL1 TKIs. The Thr315Ile mutation confers resistance to all BCR::ABL1 TKIs other than the more potent, third-generation TKIs ponatinib and asciminib. Patients with the Thr315Ile mutation have poor outcomes and can be considered for allogeneic HSCT. The best outcomes have been observed with early, daily, and continuous administration of more potent TKIs (eg, dasatinib, nilotinib, and ponatinib), in combination with intensive chemotherapy, and initially, with allogeneic HSCT in first complete remission.[79,80] However, excellent outcomes and improved toxicity were recently demonstrated with the combination of blinatumomab and dasatinib or ponatinib, shifting the framework for the treatment of Ph-positive ALL.[14,19]

Intensive chemotherapy, most often the hyper-CVAD regimen (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose cytarabine and methotrexate), combined with imatinib or second-generation TKIs (ie, dasatinib and nilotinib) elicited modest 5-year OS rates of 40–65%.[81,82] In this setting, relapse is often driven by

	Management	4-year to 5-year survival (%)
Ph-positive ALL[17,64,65]	Hyper-CVAD with TKI; TKI maintenance; allogenic HSCT in complete remission 1; non-chemotherapy regimens with TKIs and blinatumomab	>75%
Adolescents and young adult ALL[8,9,66]	Augmented BFM; hyper-CVAD with CD19, CD20, or CD22 antibodies	60–<70%
CD20-positive ALL[67,66,68]	ALL chemotherapy with CD19, CD20, or CD22 antibodies	60–<70%
Ph-like ALL[69,70]	Hyper-CVAD with TKI or antibody	60–70%
T-cell ALL (except ETP-ALL)[59,71,72]	High doses cyclophosphamide; high doses cytarabine; asparaginase; nelarabine; venetoclax	>60%
Older ALL (age 60 years and older)[73]	Mini-hyper-CVD plus inotuzumab ozogamicin and blinatumomab	50%
MRD-positive ALL by MFC or NGS[74,75]	Prognosis is worse; blinatumomab with or without allogeneic HSCT in complete remission 1 (might not be the case if MRD-negativity by NGS)	Improved from less than 20% to 40–50% with the addition of blinatumomab
Allogeneic HSCT in complete remission 1[70,76,77]	ETP-ALL; *KMT2A*-rearranged ALL; complex cytogenetics (≥5 abnormalities); low hypodiploidy or near triploidy; Ph-like ALL with *CRLF2* or *JAK* mutations	50–60%

ALL=acute lymphocytic leukaemia. BFM=Berlin–Frankfurt–Munster. ETP=early T-cell precursor. HSCT=haematopoietic stem cell transplantation. Hyper-CVAD=hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose cytarabine and methotrexate. MRD=measurable residual disease. NGS=next-generation sequencing. Ph=Philadelphia chromosome. TKI=tyrosine-kinase inhibitor.

Table 1: **Summary of therapies for acute lymphocytic leukaemia by subtype**

	Notable toxic effects	Management strategies
Cytotoxic chemotherapy regimen or agent		
Hyper-CVAD	Myelosuppression; peripheral neuropathy, constipation (vincristine); hypertension, hyperglycaemia, steroid-psychosis (glucocorticoids); avascular necrosis (glucocorticoids, mainly in paediatrics); renal impairment (high-dose methotrexate); cerebellar toxic effects (high-dose cytarabine); fever, rash, ocular toxic effects (high-dose cytarabine)	Antimicrobial prophylaxis during times of neutropenia; growth factor support; neuropathy assessment before each course; bowel regimen during vincristine courses; enhance blood pressure monitoring and antihypertensive regimen, if indicated, during steroid courses; enhanced blood glucose monitoring and insulin support, if indicated, during steroid courses; systemic steroid pre-medication before cytarabine administration and eye drops for the following 2 days; urine alkalinisation, methotrexate level monitoring, and leucovorin rescue during and after high-dose methotrexate administration
Asparaginase	Hyperglycaemia; hepatotoxicity (increased AST, ALT, or bilirubin); hypersensitivity reaction; pancreatitis; thrombosis	Enhanced blood glucose monitoring and insulin support, if indicated, during asparaginase-containing courses; regular liver function test and coagulation monitoring
Nelarabine	Peripheral neuropathy; central neurotoxicity (somnolence); rhabdomyolysis (rare)	Neuropathy assessment before each course; avoid intrathecal therapy during nelarabine courses; avoid excessive exercise during nelarabine courses
Monoclonal antibodies		
Blinatumomab	Cytokine release syndrome; neurotoxicity (eg, tremor, difficulty writing, or aphasia); elevated AST or ALT	Steroid pre-medication before initiation and dose escalation; neurological assessment at initiation, escalation, and throughout treatment
Inotuzumab ozogamicin	Thrombocytopenia; sinusoidal obstructive syndrome	Regular complete blood count and CMP monitoring; ursodiol prophylaxis throughout treatment
BCR::ABL1 tyrosine-kinase inhibitors		
Imatinib	Oedema; myalgias	..
Dasatinib	Pleural and pericardial effusion; pulmonary hypertension; oedema	Diuresis; prednisone if there is considerable effusion; dose reduction
Nilotinib	QTc prolongation; pancreatitis; hyperglycaemia; vaso-occlusive events	Avoid concomitant QTc-prolonging medications; increase blood glucose monitoring upon initiation and maintain regular monitoring with continued use; avoid in patients with considerable cardiac history
Ponatinib	Hypertension; hepatotoxicity; pancreatitis; arterial and venous occlusive events	Optimise hypertension management before initiation; regular CMP monitoring; consider low-dose statin and aspirin 81 mg if tolerable

Most toxic effects specific to each BCR::ABL1 tyrosine kinase inhibitor can be managed with supportive care and with dose reduction under close monitoring of the treating leukaemia physician. ALT=alanine aminotransferase. AST=aspartate aminotransferase. CMP=comprehensive metabolic panel. Hyper-CVAD=hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose cytarabine and methotrexate. QTc=corrected QT interval.

Table 2: **Common toxic effects and management strategies for acute lymphocytic leukaemia therapies**

See Online for appendix

the emergence of Thr315Ile *ABL1* kinase domain mutations, responsible for 75% of relapses. Use of the third-generation TKI ponatinib in combination with hyper-CVAD has led to superior outcomes, including a 6-year OS rate of 70%.[63,80,83] The PONALFIL trial (NCT02776605) also showed superior outcomes with the use of ponatinib (4-year OS rate 92%)[84] compared with historical results for imatinib (3-year OS rate 53%).

The multicentre phase 3 PhALLCON trial (NCT03589326) randomised newly diagnosed patients with Ph-positive ALL to receive low-intensity chemotherapy plus either ponatinib 30 mg daily or imatinib 600 mg daily.[20] Ponatinib was associated with higher rates of MRD-negative complete remission at the end of induction (34% *vs* 17%, p=0·002), and deep molecular responses (42% *vs* 21%).[20] These findings led to the regulatory approval of ponatinib as front-line therapy for Ph-positive ALL in March, 2024.

The activity of blinatumomab as a single agent in patients with relapsed or refractory Ph-positive ALL[85] prompted the evaluation of this combination in the front-line setting (appendix p 1). In the D-ALBA trial (NCT02744768), dasatinib and steroids were given for 85 days, followed by the addition of blinatumomab to continuous dasatinib along with 12 doses of intrathecal chemotherapy prophylaxis.[17] Long-term follow-up showed an OS rate of 81%.[17] A single-group trial evaluated the simultaneous combination of ponatinib and blinatumomab in the front-line setting.[19] Unlike the D-ALBA trial, ponatinib and blinatumomab were started together at induction, with blinatumomab given in five courses. Among 60 patients treated (median age 60 years; range 20–83 years), the complete molecular response rate was 83%, and the MRD-negativity rate was 98% by NGS (sensitivity 1×10^{-6}).[64] Only two patients underwent allogeneic HSCT in first complete remission (detectable *BCR::ABL1* transcripts 0·01–0·05%). The 3-year EFS rate was 77%, and the 3-year OS rate was 91%.[64] The concomitant combination of blinatumomab and ponatinib appears to improve outcomes and reduce the

need for allogeneic HSCT in the front-line setting (appendix p 1).

Several studies have suggested that allogeneic HSCT might offer limited benefit to patients who have a major molecular response by 3 months or later, that having a 3-month complete molecular response in patients not undergoing allogenic HSCT is associated with better OS, and that ponatinib might be more effective than other TKIs.[86–90] Using NGS could further define patients who should be considered for allogeneic HSCT given the discordance observed between NGS and PCR testing. NGS might detect MRD positivity in approximately 10% of patients who are MRD-negative by PCR, while up to 30% of patients who are MRD-positive by PCR could be MRD-negative by NGS.[74] In the future, NGS might serve as the primary tool for assessing MRD in Ph-positive disease; however, more robust data on the prognostic effect of NGS versus PCR testing are needed.

Ph-negative pre-B-cell ALL

Adult regimens for Ph-negative pre-B-cell ALL have historically differed from paediatric approaches, which emphasise prolonged corticosteroid use and the incorporation of asparaginase. In contrast, adult protocols often feature reduced treatment intensity, shorter maintenance durations, and a greater reliance on myelosuppressive agents and allogeneic and autologous HSCT. However, studies comparing paediatric and adult regimens have shown the superior efficacy of paediatric-inspired approaches, particularly in adolescents and young adults (age 15–39 years),[91–94] giving a 5-year OS of 65%.[94] The hyper-CVAD regimen, developed in 1992, was as active as paediatric-inspired regimens, but differs in that it de-emphasises the use of asparaginase and relies on cytotoxic agents associated with more myelosuppression-related complications. In contrast, paediatric-inspired regimens are associated with more asparaginase-related complications (eg, thrombosis, pancreatitis, and liver dysfunction).[8,9,95] The adult regimens, particularly hyper-CVAD, have evolved during more than two decades by incorporating novel monoclonal antibodies into the cytotoxic chemotherapy backbone in an effort to continue to improve outcomes while maintaining safety in adult patients with B-cell ALL. This progression in treatment began with the addition of the CD20 monoclonal antibody rituximab and most recently included the CD22 antibody drug conjugate inotuzumab ozogamicin and the CD19 BiTE blinatumomab. Adding rituximab to the hyper-CVAD regimen improved OS[39] and led to a significant improvement in EFS in the phase 3 GRAALL-R 2005 trial (2-year EFS rate 65% *vs* 52%, p=0·038) when compared with standard chemotherapy alone.[96]

Blinatumomab has revolutionised the treatment of B-cell ALL since a significant improvement in OS was shown in the phase 3 TOWER study (NCT02013167) compared with conventional chemotherapy in patients with relapsed B-cell ALL (median OS 7·7 months *vs* 4·0 months, p=0·01).[12] Blinatumomab has since improved outcomes in patients with both MRD-positive and MRD-negative B-cell ALL, and is therefore being incorporated into both paediatric-inspired and adult front-line regimens (appendix p 2).[22,97] A single-group trial investigated the sequential use of hyper-CVAD plus blinatumomab, and the later addition of inotuzumab.[98] In a cohort of 75 patients, the complete remission rate was 100% with an NGS–MRD-negative rate of 73% and a 4-year OS rate of 89%.[67,98] The benefit of blinatumomab in newly diagnosed Ph-negative B-cell ALL was shown in the E1910 study, which randomly assigned 224 patients who had MRD negativity after front-line paediatric-inspired chemotherapy to receive consolidation with either chemotherapy plus blinatumomab (four cycles) or standard chemotherapy. Blinatumomab consolidation significantly improved OS: median OS not reached versus 71·4 months (p=0·0003), and the 3-year OS was 85% versus 68%.[22]

Treating older adults (age ≥60 years) with Ph-negative ALL is also difficult.[76,99] Historically, long-term OS was 20% or less with intensive chemotherapy due to adverse cytogenetic and molecular features, leading to high rates of induction mortality and death in remission.[8,9,99–101] As a result, low-intensity regimens omitting or considerably reducing the doses of traditional chemotherapy agents have been explored with limited success. Similar to blinatumomab, single-agent inotuzumab also improved OS compared with conventional chemotherapy in the phase 3 INO-VATE trial (median OS 7·7 months *vs* 6·2 months, p=0·04).[13] Consequently, inotuzumab has been integrated into numerous lower-intensity regimens studied in older patients to replace more toxic traditional chemotherapy agents. One such regimen includes the mini-hyper-CVD regimen (low-dose hyper-fractionated cyclophosphamide, vincristine, and dexamethasone), which significantly reduces the doses of the chemotherapy agents found in the traditional hyper-CVAD regimen and also omits doxorubicin, while adding inotuzumab and subsequently blinatumomab in a sequential manner.[102] This regimen showed an overall response rate (ORR) of 99% and a 5-year OS of 46% among 80 older patients (median age 68 years, range 60–87 years) with B-cell ALL.[73,94] The Alliance A041703 study also resulted in an ORR of 97% and 1-year EFS and OS of 75% and 74%, respectively, using inotuzumab plus blinatumomab (with minimal chemotherapy) in older (age ≥60 years) patients with B-cell ALL.[103] Other studies combining low-dose chemotherapy with inotuzumab or blinatumomab in older patients with newly diagnosed ALL showed superior outcomes compared with historical data (appendix p 3).

T-cell ALL

Among the T-cell ALL subtypes, ETP-ALL is considered high risk, characterised by high rates of relapse and thus benefits from allogeneic HSCT in first complete

remission.[104–107] Improving outcomes in T-cell ALL has been particularly challenging due to the limited availability of targeted therapies, relying instead on modified chemotherapies (eg, high-dose cytarabine, methotrexate, asparaginase, and nelarabine). Inspired by preclinical studies showing the activity of the BH3-mimetics (eg, venetoclax and navitoclax) in T-cell ALL, these agents are now being developed in adult T-cell ALL.[58,108] The hyper-CVAD regimen combined with nelarabine, asparaginase, and venetoclax showed a 5-year OS of 64%.[78] In older patients, the combination of venetoclax and low-intensity chemotherapy yielded MRD-negative complete remission rates of 83%.[108,109] CAR T cells targeting T-cell ALL are also being investigated.[110] Harnessing and redirecting normal T cells to recognise and eliminate malignant T lymphoblasts was initially challenging, but several innovative strategies have addressed these obstacles.[111,112] CD7 CAR T cells have shown promising results, including an MRD-negative complete remission rate of 96% and a 2-year OS of 63%.[110] Ongoing clinical trials evaluating CAR T-cell therapy in T-cell ALL are summarised in the appendix (p 4).

Special considerations

BCR::ABL1-like ALL

BCR::ABL1-like ALL accounts for 25% of B-cell ALL in young adults (age 21–39 years).[37,113] About 70–80% of *BCR::ABL1*-like ALL cases have *CRLF2* overexpression; 50% also harbour *JAK* mutations and have a worse prognosis even with novel regimens. Around 20–30% have *ABL*-class fusions, including *ABL1* or *PDGFR* translocations, and might benefit from the incorporation of a BCR::ABL1 TKI into their treatment regimen.[69,114] *CRLF2* or *JAK* alterations in *BCR::ABL1*-like ALL define a high-risk ALL that might necessitate allogeneic HSCT in first complete remission[69,70,113] as these mutations are more resistant to standard chemotherapy and are associated with poor OS of 20–30%.[70] In the phase 3 TOWER study, blinatumomab was shown to be highly active in *BCR::ABL1*-like ALL.[115] Targeted therapies, such as dasatinib for *ABL1* gene alterations[116,117] and front-line immunotherapy, could improve outcomes in these patients.[67,70,98]

CNS prophylaxis and management of CNS relapses

The CNS is a sanctuary site for ALL cells, making CNS monitoring and disease prevention a major component of ALL therapy. Although primary CNS involvement at diagnosis is relatively uncommon (<5–10%), relapse rates can reach up to 75% without prophylactic treatment.[25,118] However, with effective CNS prophylaxis, this risk drops to lower than 10%.[119] An increased risk of CNS disease has been observed in Ph-positive ALL, particularly following the substantial improvement in OS achieved with the addition of TKIs to chemotherapy, resulting in late and isolated CNS relapses in 10–15% of patients.[80,81,120]

High-dose intravenous methotrexate and cytarabine can penetrate the CNS but are insufficient to fully eradicate leukaemia cells within the CNS. Therefore, intrathecal chemotherapy using methotrexate, cytarabine, or triple intrathecal therapy (ie, methotrexate, hydrocortisone, and cytarabine) is an essential component of CNS prophylaxis. Depending on the treatment protocol, patients typically receive between eight and 17 doses of prophylactic intrathecal chemotherapy.[43,64,94,121,122] The effectiveness of intrathecal and systemic therapy have made prophylactic cranial irradiation unnecessary in both adult and paediatric ALL, thereby avoiding radiation-associated complications.[25,118,120,122]

Newly diagnosed patients with CNS leukaemia are treated with standard systemic chemotherapy along with intensified triple intrathecal therapies until cerebrospinal fluid blasts are cleared, followed by at least 8–12 more intrathecal treatments after clearance. In this setting, survival outcomes are comparable to CNS-negative patients.[25,40,123,124]

As lower-intensity regimens and chemotherapy-free approaches (eg, blinatumomab and inotuzumab) become more common, the risk of CNS relapses can increase, necessitating more frequent intrathecal chemotherapies. Salvage regimens should include systemic chemotherapy and CNS-penetrating agents, such as high-dose methotrexate and cytarabine,[100] in addition to triple intrathecal therapies. For patients with CNS disease, a common practice is to administer triple intrathecal therapies twice per week until CNS clearance, followed by weekly doses for 4–8 weeks, and then every other week for an additional 4–8 doses. Radiation therapy is typically reserved for patients who are unresponsive to triple intrathecal therapy.[40]

CAR T-cell therapy has shown efficacy for CNS relapse, with a CNS remission rate of 85% in relapsed or refractory B-cell ALL. The 12-month CNS relapse rate was 11%.[125] An analysis of the combined data from five studies also supports the benefit of CAR T cells for treating CNS relapse.[51] Future trials will explore CAR T-cell consolidation for patients at high risk of CNS relapse.

Monitoring MRD and its management

Persistent MRD in complete remission is a considerable adverse prognostic factor in adult and paediatric ALL, in both Ph-positive and Ph-negative disease. A meta-analysis showed that undetectable MRD in complete remission was associated with favourable outcomes: hazard ratio 0·28 for EFS and OS with a 10-year OS of 60% for undetectable MRD compared with 15% for persistent MRD.[126] MRD should be measured at crucial milestones—ie, post-induction complete remission, 3–4 months into therapy, then every 3–6 months.

Current MRD detection methods include multi-parameter flow cytometry (MFC), RT-PCR, and NGS.[127] MFC, although widely available, has lower sensitivity (10^{-4} cells) compared with molecular methods. Highly

sensitive (10^{-4} to 10^{-5} cells) RT-PCR is used to quantify *BCR::ABL1* transcripts in Ph-positive ALL[128] and MRD in Ph-negative and T-cell ALL.[34,75] NGS assays are used to track the leukaemia-specific immunoglobin heavy chain variable region or T-cell receptor gene rearrangements at a sensitivity of 1×10^{-6} cells, 1–2 log greater than standard MFC or PCR assays.[34,75]

Discordance between assays due to different methods of testing and sensitivity has been shown in both Ph-positive and Ph-negative disease. A recent analysis in Ph-positive ALL showed that 11% of patients who had NGS–MRD negativity still had detectable *BCR::ABL1* transcripts by RT-PCR.[74] However, among patients who had NGS–MRD negativity, the presence or absence of *BCR::ABL1* transcripts by RT-PCR did not affect prognosis, suggesting that the persistent *BCR::ABL1* transcripts did not represent true lymphocytic MRD. Having NGS–MRD negativity was associated with a very low risk of relapse, despite persistently detectable *BCR::ABL1* transcripts by RT-PCR.[74] Therefore, persistent low-level *BCR::ABL1* transcripts by RT-PCR should not be used to decide treatment escalation, in particular, allogeneic HSCT. Such decisions should be based on the NGS–MRD results if available.

Comparing NGS–MRD (sensitivity 1×10^{-6} cells) with MFC (sensitivity 10^{-4} cells) showed that among patients with Ph-negative B-cell ALL or T-cell ALL who were MFC–MRD negative, 46% were NGS–MRD positive.[129] In patients who were NGS–MRD negative at complete remission, the 5-year relapse rate was 0% and the 5-year OS was 90%. Thus, MRD monitoring with a highly sensitive assay is useful in identifying patients at low risk to receive low-intensity treatment or for patients at high risk who might need intensification of therapy, such as CAR T cells or allogeneic HSCT. Modern MFC assays have an increased sensitivity beyond 10^{-4} cells, reaching up to 2×10^{-6} cells, consequently comparative studies of NGS with highly sensitive MFC are needed to understand the optimal technique for MRD monitoring in the future.

In patients with MRD-positive B-cell ALL, blinatumomab leads to MRD negativity in 78% of patients after one cycle of treatment, resulting in superior relapse-free survival and OS compared with those with persistent MRD.[86] Blinatumomab is approved for patients with MRD 0·1% or higher, and is effective in lower-burden disease.[129] Whether patients with MRD response after blinatumomab require a consolidative allogeneic HSCT (*vs* CAR T cells) is under investigation.[129]

After completion of all therapies, patients should be followed regularly by their general provider, annually or more frequently if indicated, for management of any comorbid conditions. Annual complete blood count, physical exam, and follow-ups are recommended to help detect any clinical relapse. Upon relapse, patients can have similar symptoms as at the time of diagnosis (ie, fever, fatigue, easy bruising, and frequent infections). Monitoring MRD allows for early detection of molecular relapse before the development of any overt signs or symptoms of relapse.

Salvage therapy

Traditional salvage chemotherapy, with or without allogeneic HSCT in second complete remission, has historically led to poor outcomes in adult ALL, with complete remission rates of 30–50% and 5-year OS less than 10%. The complete remission rates for later salvage therapies drop to less than 20%. Consequently, enrolment on a clinical trial is recommended for patients with relapsed ALL to improve outcomes with novel therapies only available on clinical trial. Similarly, whether children with relapsed ALL should also be enrolled on a clinical trial with treatment depends on the site of relapse, time of relapse, immunophenotype, genotype, and previous treatments.

Chemotherapy salvage combinations in adults depend on the front-line therapy exposures and duration of first complete remission. In general, hyper-CVAD, fludarabine, high-dose cytarabine–idarubicin, and methotrexate–asparaginase regimens could serve as the chemotherapy backbones to which additional agents could be added. Immunotherapies, including antibodies targeting CD19 and CD22 and CAR T cells have considerably improved outcomes in relapsed-refractory B-cell ALL.[12,13,130] In Ph-positive ALL, combinations of ponatinib, blinatumomab, and intensive chemotherapy, followed by CAR T cells or allogeneic HSCT, and post-HSCT TKI maintenance, might result in high complete remission and survival rates. In a report of 22 patients who relapsed after receiving ponatinib in the front-line setting, 90% of patients had a second complete remission and 28% proceeded to allogeneic HSCT. The median relapse-free survival was 14·7 months and the median survival 22·6 months.[11]

For patients with relapsed or refractory T-cell ALL who are nelarabine-naive, nelarabine-based regimens could be effective, and BCR::ABL1 TKIs can be used if *ABL*-class fusions, mostly *NUP214::ABL1*, *EML1::ABL1*, and *ETV6::ABL1* are identified.[8,9]

Combination therapies with blinatumomab and inotuzumab ozogamicin

Blinatumomab and inotuzumab ozogamicin are each approved for the treatment of relapsed B-cell ALL as single agents. However, the OS benefit was modest in the randomised trials compared with intensive chemotherapy combinations (median OS 7·7 months with either modality, OS 25% or less at 2–3 years).[12,13] Optimal outcomes with these agents in the relapsed setting can be achieved with combination therapy rather than using either of these agents alone.[131]

The mini-hyper-CVD regimen incorporating both blinatumomab and inotuzumab showed an ORR of 83% and a 3-year OS of 52% among 110 patients with relapsed B-cell ALL.[131,132] A notable but rare adverse effect associated

with inotuzumab is sinusoidal obstructive syndrome (SOS). Pharmacokinetic and pharmacodynamic studies have shown that fractionated lower-dose administration of inotuzumab provides similar efficacy while significantly reducing the risk of SOS.[133,134] Consequently, the mini-hyper-CVD regimen was modified to incorporate this fractionated dosing strategy. Among patients treated with the original dosing schedule, nine (13%) of 67 developed SOS, compared with only one (2%) in 43 among those who received the fractionated lower-dose schedule (p=0·02). Using a dose-dense regimen incorporating inotuzumab and blinatumomab into the chemotherapy courses could further improve outcomes.[135]

A new subcutaneous blinatumomab formulation is under investigation and could provide convenience and improve efficacy by delivering higher drug doses compared with intravenous blinatumomab. In a phase 1b expansion trial in heavily pretreated relapsed or refractory B-cell ALL, subcutaneous blinatumomab resulted in a complete remission rate of 89%, and MRD-negative rate of 91% among the responders.[136] If the efficacy and safety of subcutaneous blinatumomab are confirmed, the combination of convenience and high efficacy could have a global impact on ALL therapy, possibly replacing intravenous blinatumomab.

CAR T-cell therapies

CAR T cells are genetically modified autologous T lymphocytes engineered to express binding sites of specific antibodies, such as a receptor against CD19.[137] Overall, CAR T-cell therapy appears to be most efficacious in patients with minimal disease at the time of cell infusion.[138] However, the manufacturing process (from pheresis to infusion) takes several weeks to months and many patients require additional salvage therapy to maintain disease control during this interval. Considerable toxic effects associated with CAR T-cell therapy include cytokine release syndrome, which correlates with disease burden and neurotoxicity. Due to the severity and complexity of these adverse effects, treatment should be administered and monitored by multidisciplinary teams who have experience with CAR T-cell products. The results of the key CAR T-cell trials in B-cell ALL are summarised in the appendix (p 5).[130,139,140]

Although high remission rates have been obtained with CD19 CAR T cells, relapses occurred in more than 50% of cases, often due to downregulation or loss of CD19 surface antigen expression on leukaemia cells and because of limited CAR T-cell persistence.[141] Clinical trials evaluating CAR T cells targeting other or dual epitopes (eg, CD19 and CD22) are ongoing.[142] The real-world CAR T-cells consortium data showed better outcomes with CAR T-cell therapy for low disease burden or no detectable disease at the time of treatment.[143,144] Consolidation with CAR T cells after remission induction with chemoimmunotherapy salvage regimens is under evaluation.

Conclusion

Considerable advancements have been made in identifying new ALL subsets, understanding the prognostic significance of MRD, and development of novel targeted therapies. The integration of more potent BCR::ABL1 TKIs, targeted antibodies, and other novel targeted therapies into the front-line regimens is showing promising outcomes, potentially signalling a shift in ALL management. Future strategies include: (1) incorporation of multiple targeted antibodies for CD19, CD20, and CD22 into a single regimen; (2) reducing chemotherapy intensity and shortening treatment duration; (3) replacing intensive chemotherapy with targeted therapies (eg, ponatinib and blinatumomab in Ph-positive ALL and blinatumomab and menin inhibitors in *KMT2A*-rearranged ALL); (4) using CAR T-cell therapies in first complete remission for patients with MRD or high-risk disease; and (5) implementing standardised NGS-based MRD monitoring to guide therapy adjustments.

Contributors

All authors contributed equally to the development of the Seminar, the review of published literature, and writing and final review of the manuscript.

Declaration of interests

HK received research grants from AbbVie, Amgen, Ascentage, Bristol Myers Squibb, Daiichi-Sankyo, Immunogen, Jazz, Novartis, and Pfizer; and honoraria from AbbVie, Amgen, Aptitude Health, Ascentage, Astellas Health, AstraZeneca, Ipsen Pharmaceuticals, KAHR Medical, NOVA Research, Novartis, Pfizer, Precision Biosciences, and Taiho Pharmaceutical Canada. C-HP serves on the scientific advisory board of Adaptive Biotechnologies; participates on the data monitoring board of Novartis; and receives honorarium from UpToDate. EJ received research grants from AbbVie, Adaptive Biotechnologies, Amgen, Pfizer, and Takeda; and consultancy fees from AbbVie, Adaptive Biotechnologies, Amgen, Bristol Myers Squibb, Genentech, Incyte, Novartis, Pfizer, and Takeda.

Acknowledgments

This work was supported by the MD Anderson Cancer Center Support Grant P30 CA016672 from the National Cancer Institute (National Institutes of Health), the Charif Souki Cancer Research Fund, the St. Jude Cancer Center Support Grant CA21765, and the American Lebanese Syrian Associated Charities.

References

1 Pui CH, Yang JJ, Hunger SP, et al. Childhood acute lymphoblastic leukemia: progress through collaboration. *J Clin Oncol* 2015; **33:** 2938–48.
2 Short NJ, Kantarjian H, Jabbour E. Optimizing the treatment of acute lymphoblastic leukemia in younger and older adults: new drugs and evolving paradigms. *Leukemia* 2021; **35:** 3044–58.
3 Hu Y, Zhang X, Zhang A, et al. Global burden and attributable risk factors of acute lymphoblastic leukemia in 204 countries and territories in 1990–2019: estimation based on Global Burden of Disease Study 2019. *Hematol Oncol* 2022; **40:** 92–104.
4 Roberts KG, Mullighan CG. Genomics in acute lymphoblastic leukaemia: insights and treatment implications. *Nat Rev Clin Oncol* 2015; **12:** 344–57.
5 Brady SW, Roberts KG, Gu Z, et al. The genomic landscape of pediatric acute lymphoblastic leukemia. *Nat Genet* 2022; **54:** 1376–89.
6 de Smith AJ, Wahlster L, Jeon S, et al. A noncoding regulatory variant in IKZF1 increases acute lymphoblastic leukemia risk in Hispanic/Latino children. *Cell Genom* 2024; **4:** 100526.

7 National Cancer Institute. Cancer stat facts: leukemia–acute lymphocytic leukemia (ALL). 2024. https://seer.cancer.gov/statfacts/html/alyl.html (accessed April 24, 2025).

8 Howlader NNA, Krapcho M, Miller D, et al, Cronin KA (eds). SEER cancer statistics review, 1975–2018. National Cancer Institute, 2021.

9 Jabbour E, Short NJ, Jain N, et al. The evolution of acute lymphoblastic leukemia research and therapy at MD Anderson over four decades. *J Hematol Oncol* 2023; **16:** 22.

10 Sasaki K, Jabbour E, Short NJ, et al. Acute lymphoblastic leukemia: a population-based study of outcome in the United States based on the surveillance, epidemiology, and end results (SEER) database, 1980-2017. *Am J Hematol* 2021; **96:** 650–58.

11 Short NJ, Jabbour E, Nasr LF, et al. Characteristics and outcomes of patients with relapsed Philadelphia chromosome-positive acute lymphoblastic leukemia after failure of a frontline ponatinib-containing therapy. *Am J Hematol* 2024; **99:** 1423–26.

12 Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med* 2017; **376:** 836–47.

13 Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med* 2016; **375:** 740–53.

14 Jabbour E, Haddad FG, Short NJ, Kantarjian H. Treatment of adults with Philadelphia chromosome–positive acute lymphoblastic leukemia–from intensive chemotherapy combinations to chemotherapy-free regimens: a review. *JAMA Oncol* 2022; **8:** 1340–48.

15 Pieters R, de Groot-Kruseman H, Fiocco M, et al. Improved outcome for ALL by prolonging therapy for *IKZF1* deletion and decreasing therapy for other risk groups. *J Clin Oncol* 2023; **41:** 4130–42.

16 Möricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood* 2008; **111:** 4477–89.

17 Foà R, Bassan R, Elia L, et al. Long-term results of the dasatinib–blinatumomab protocol for adult Philadelphia-positive ALL. *J Clin Oncol* 2024; **42:** 881–85.

18 Shen S, Chen X, Cai J, 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:** 358–66.

19 Jabbour E, Short NJ, Jain N, et al. Ponatinib and blinatumomab for Philadelphia chromosome-positive acute lymphoblastic leukaemia: a US, single-centre, single-arm, phase 2 trial. *Lancet Haematol* 2023; **10:** e24–34.

20 Jabbour E, Kantarjian HM, Aldoss I, et al. Ponatinib vs imatinib in frontline Philadelphia chromosome-positive acute lymphoblastic leukemia: a randomized clinical trial. *JAMA* 2024; **331:** 1814–23.

21 van der Sluis IM, de Lorenzo P, Kotecha RS, et al. Blinatumomab added to chemotherapy in infant lymphoblastic leukemia. *N Engl J Med* 2023; **388:** 1572–81.

22 Litzow MR, Sun Z, Mattison RJ, et al. Blinatumomab for MRD-negative acute lymphoblastic leukemia in adults. *N Engl J Med* 2024; **391:** 320–33.

23 Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. *N Engl J Med* 2004; **350:** 1535–48.

24 Jabbour E, O'Brien S, Konopleva M, Kantarjian H. New insights into the pathophysiology and therapy of adult acute lymphoblastic leukemia. *Cancer* 2015; **121:** 2517–28.

25 Thastrup M, Duguid A, Mirian C, Schmiegelow K, Halsey C. Central nervous system involvement in childhood acute lymphoblastic leukemia: challenges and solutions. *Leukemia* 2022; **36:** 2751–68.

26 Kuroda Y, Fujiyama F, Ohyama T, et al. Numb chin syndrome secondary to Burkitt's cell acute leukemia. *Neurology* 1991; **41:** 453–54.

27 Pölönen P, Di Giacomo D, Seffernick AE, et al. The genomic basis of childhood T-lineage acute lymphoblastic leukaemia. *Nature* 2024; **632:** 1082–91.

28 Bloom M, Maciaszek JL, Clark ME, Pui C-H, Nichols KE. Recent advances in genetic predisposition to pediatric acute lymphoblastic leukemia. *Expert Rev Hematol* 2020; **13:** 55–70.

29 Gocho Y, Yang JJ. Genetic defects in hematopoietic transcription factors and predisposition to acute lymphoblastic leukemia. *Blood* 2019; **134:** 793–97.

30 Yang H, Zhang H, Luan Y, et al. Noncoding genetic variation in GATA3 increases acute lymphoblastic leukemia risk through local and global changes in chromatin conformation. *Nat Genet* 2022; **54:** 170–79.

31 Gocho Y, Liu J, Hu J, et al. Network-based systems pharmacology reveals heterogeneity in LCK and BCL2 signaling and therapeutic sensitivity of T-cell acute lymphoblastic leukemia. *Nat Cancer* 2021; **2:** 284–99.

32 Brown P, Inaba H, Annesley C, et al. Pediatric acute lymphoblastic leukemia, version 2.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2020; **18:** 81–112.

33 Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia* 2022; **36:** 1720-48.

34 Gökbuget N, Boissel N, Chiaretti S, et al. Diagnosis, prognostic factors, and assessment of ALL in adults: 2024 ELN recommendations from a European expert panel. *Blood* 2024; **143:** 1891–902.

35 Chang T-C, Chen W, Qu C, et al. Genomic determinants of outcome in acute lymphoblastic leukemia. *J Clin Oncol* 2024; **42:** 3491–503.

36 Pieters R, Mullighan CG, Hunger SP. Advancing diagnostics and therapy to reach universal cure in childhood ALL. *J Clin Oncol* 2023; **41:** 5579–91.

37 Pui CH, Roberts KG, Yang JJ, Mullighan CG. Philadelphia chromosome-like acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk* 2017; **17:** 464–70.

38 Perez-Andreu V, Roberts KG, Harvey RC, et al. Inherited GATA3 variants are associated with Ph-like childhood acute lymphoblastic leukemia and risk of relapse. *Nat Genet* 2013; **45:** 1494–98.

39 Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer* 2006; **106:** 1569–80.

40 Pui C-H, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med* 2009; **360:** 2730–41.

41 Jeha S, Pei D, Choi J, et al. Improved CNS control of childhood acute lymphoblastic leukemia without cranial irradiation: St Jude total therapy study 16. *J Clin Oncol* 2019; **37:** 3377–91.

42 Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. *Lancet Oncol* 2012; **13:** 936–45.

43 Hunger SP, Tran TH, Saha V, et al. Dasatinib with intensive chemotherapy in de novo paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia (CA180-372/COG AALL1122): a single-arm, multicentre, phase 2 trial. *Lancet Haematol* 2023; **10:** e510–20.

44 Moorman AV, Schwab C, Winterman E, et al. Adjuvant tyrosine kinase inhibitor therapy improves outcome for children and adolescents with acute lymphoblastic leukaemia who have an ABL-class fusion. *Br J Haematol* 2020; **191:** 844–51.

45 Brown PA, Ji L, Xu X, et al. Effect of postreinduction therapy consolidation with blinatumomab vs chemotherapy on disease-free survival in children, adolescents, and young adults with first relapse of B-cell acute lymphoblastic leukemia: a randomized clinical trial. *JAMA* 2021; **325:** 833–42.

46 Locatelli F, Zugmaier G, Rizzari C, et al. Effect of blinatumomab vs chemotherapy on event-free survival among children with high-risk first-relapse B-cell acute lymphoblastic leukemia: a randomized clinical trial. *JAMA* 2021; **325:** 843–54.

47 Gupta S, Rau RE, Kairalla JA, et al. Blinatumomab in standard-risk B-cell acute lymphoblastic leukemia in children. *N Engl J Med* 2025; **392:** 875–91.

48 Hodder A, Mishra AK, Connor P, et al. Blinatumomab with de-escalated chemotherapy for infant *KMT2A*-rearranged B-cell acute lymphoblastic leukemia. *Blood* 2024; **144** (suppl 1)**:** 2816.

49 O'Brien MM, Ji L, Shah NN, et al. Phase II trial of inotuzumab ozogamicin in children and adolescents with relapsed or refractory B-cell acute lymphoblastic leukemia: Children's Oncology Group protocol AALL1621. *J Clin Oncol* 2022; **40:** 956–67.

50 Brivio E, Locatelli F, Lopez-Yurda M, et al. A phase 1 study of inotuzumab ozogamicin in pediatric relapsed/refractory acute lymphoblastic leukemia (ITCC-059 study). *Blood* 2021; **137:** 1582–90.

51 Leahy AB, Newman H, Li Y, et al. CD19-targeted chimeric antigen receptor T-cell therapy for CNS relapsed or refractory acute lymphocytic leukaemia: a post-hoc analysis of pooled data from five clinical trials. *Lancet Haematol* 2021; **8:** e711–22.

52 Laetsch TW, Maude SL, Rives S, et al. Three-year update of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia in the ELIANA Trial. *J Clin Oncol* 2023; **41:** 1664–69.

53 Wang T, Tang Y, Cai J, et al. Coadministration of CD19- and CD22-directed chimeric antigen receptor T-cell therapy in childhood B-cell acute lymphoblastic leukemia: a single-arm, multicenter, phase II trial. *J Clin Oncol* 2023; **41:** 1670–83.

54 Ghorashian S, Jacoby E, De Moerloose B, et al. Tisagenlecleucel therapy for relapsed or refractory B-cell acute lymphoblastic leukaemia in infants and children younger than 3 years of age at screening: an international, multicentre, retrospective cohort study. *Lancet Haematol* 2022; **9:** e766–75.

55 Pulsipher MA, Han X, Maude SL, et al. Next-generation sequencing of minimal residual disease for predicting relapse after tisagenlecleucel in children and young adults with acute lymphoblastic leukemia. *Blood Cancer Discov* 2022; **3:** 66–81.

56 Hu J, Jarusiewicz J, Du G, et al. Preclinical evaluation of proteolytic targeting of LCK as a therapeutic approach in T cell acute lymphoblastic leukemia. *Sci Transl Med* 2022; **14:** eabo5228.

57 He Y, Zhang J, Zhang Y, et al. Dasatinib-therapy induced sustained remission in a child with refractory TCF7-SPI1 T-cell acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2022; **69:** e29724.

58 Pullarkat VA, Lacayo NJ, Jabbour E, et al. Venetoclax and navitoclax in combination with chemotherapy in patients with relapsed or refractory acute lymphoblastic leukemia and lymphoblastic lymphoma. *Cancer Discov* 2021; **11:** 1440–53.

59 Dunsmore KP, Winter SS, Devidas M, et al. Children's Oncology Group AALL0434: a phase III randomized clinical trial testing nelarabine in newly diagnosed T-cell acute lymphoblastic leukemia. *J Clin Oncol* 2020; **38:** 3282–93.

60 Bhatla T, Hogan LE, Teachey DT, et al. Daratumumab in pediatric relapsed/refractory acute lymphoblastic leukemia or lymphoblastic lymphoma: the DELPHINUS study. *Blood* 2024; **144:** 2237–47.

61 Oh BLZ, Shimasaki N, Coustan-Smith E, et al. Fratricide-resistant CD7-CAR T cells in T-ALL. *Nat Med* 2024; **30:** 3687–96.

62 Chiesa R, Georgiadis C, Syed F, et al. Base-edited CAR7 T cells for relapsed T-cell acute lymphoblastic leukemia. *N Engl J Med* 2023; **389:** 899–910.

63 Jabbour E, Short NJ, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. *Lancet Haematol* 2018; **5:** e618–27.

64 Kantarjian H, Short NJ, Haddad FG, et al. Results of the simultaneous combination of ponatinib and blinatumomab in Philadelphia chromosome-positive ALL. *J Clin Oncol* 2024; **24:** 4246–51.

65 Sasaki K, Jabbour EJ, Ravandi F, et al. Hyper-CVAD plus ponatinib versus hyper-CVAD plus dasatinib as frontline therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: a propensity score analysis. *Cancer* 2016; **122:** 3650–56.

66 Jabbour E, Richard-Carpentier G, Sasaki Y, et al. Hyper-CVAD regimen in combination with ofatumumab as frontline therapy for adults with Philadelphia chromosome-negative B-cell acute lymphoblastic leukaemia: a single-arm, phase 2 trial. *Lancet Haematol* 2020; **7:** e523–33.

67 Kantarjian H, Short NJ, Jain N, et al. Hyper-CVAD and sequential blinatumomab without and with inotuzumab in young adults with newly diagnosed Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia. *Am J Hematol* 2025; **100:** 402–07.

68 Sasaki K, Kantarjian HM, Morita K, et al. Hyper-CVAD plus ofatumumab versus hyper-CVAD plus rituximab as frontline therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: a propensity score analysis. *Cancer* 2021; **127:** 3381–89.

69 Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. *Blood* 2017; **129:** 572–81.

70 Senapati J, Jabbour E, Short NJ, et al. Long-term outcomes of newly diagnosed CRLF2 rearranged B-cell ALL. *J Clin Oncol* 2022; **40** (suppl)**:** 7040.

71 Senapati J, Kantarjian HM, Jabbour E, et al. Nelarabine (NEL), pegylated asparginase (PEG) and venetoclax (VEN) incorporated to HCVAD chemotherapy in the frontline treatment of adult patients with T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma (T-ALL/T-LBL). *Blood* 2023; **142** (suppl 1)**:** 963.

72 Abaza Y, M Kantarjian H, Faderl S, et al. Hyper-CVAD plus nelarabine in newly diagnosed adult T-cell acute lymphoblastic leukemia and T-lymphoblastic lymphoma. *Am J Hematol* 2018; **93:** 91–99.

73 Jabbour E, Short NJ, Senapati J, et al. Mini-hyper-CVD plus inotuzumab ozogamicin, with or without blinatumomab, in the subgroup of older patients with newly diagnosed Philadelphia chromosome-negative B-cell acute lymphocytic leukaemia: long-term results of an open-label phase 2 trial. *Lancet Haematol* 2023; **10:** e433–44.

74 Short NJ, Jabbour E, Macaron W, et al. Ultrasensitive NGS MRD assessment in Ph+ ALL: prognostic impact and correlation with RT-PCR for BCR:ABL1. *Am J Hematol* 2023; **98:** 1196–203.

75 Short NJ, Kantarjian H, Ravandi F, et al. High-sensitivity next-generation sequencing MRD assessment in ALL identifies patients at very low risk of relapse. *Blood Adv* 2022; **6:** 4006–14.

76 Senapati J, Kantarjian H, Haddad FG, et al. SOHO state of the art updates and next questions | next questions: acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk* 2024; **24:** 333–39.

77 Prockop S, Wachter F. The current landscape: allogeneic hematopoietic stem cell transplant for acute lymphoblastic leukemia. *Best Pract Res Clin Haematol* 2023; **36:** 101485.

78 Ravandi F, Senapati J, Jain N, et al. Longitudinal follow up of a phase 2 trial of venetoclax added to hyper-CVAD, nelarabine and pegylated asparaginase in patients with T-cell acute lymphoblastic leukemia and lymphoma. *Leukemia* 2024; **38:** 2717–21.

79 Ravandi F, Othus M, O'Brien SM, et al. US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive ALL. *Blood Adv* 2016; **1:** 250–59.

80 Kantarjian H, Short NJ, Jain N, et al. Frontline combination of ponatinib and hyper-CVAD in Philadelphia chromosome-positive acute lymphoblastic leukemia: 80-months follow-up results. *Am J Hematol* 2023; **98:** 493–501.

81 Ravandi F, O'Brien SM, Cortes JE, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer* 2015; **121:** 4158–64.

82 Daver N, Thomas D, Ravandi F, et al. Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Haematologica* 2015; **100:** 653–61.

83 Kantarjian HM, Chifotides HT, Haddad FG, Short NJ, Loghavi S, Jabbour E. Ponatinib–review of historical development, current status, and future research. *Am J Hematol* 2024; **99:** 1576–85.

84 Ribera JM, Morgades M, Ribera J, et al. PONALFIL trial for adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: long-term results. *HemaSphere* 2024; **8:** e67.

85 Martinelli G, Boissel N, Chevallier P, et al. Complete hematologic and molecular response in adult patients with relapsed/refractory Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: results from a phase II, single-arm, multicenter study. *J Clin Oncol* 2017; **35:** 1795–802.

86 Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. *Blood* 2015; **125:** 3711–19.

87 Short NJ, Jabbour E, Sasaki K, et al. Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 2016; **128:** 504–07.

88 Sasaki K, Kantarjian HM, Short NJ, et al. Prognostic factors for progression in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia in complete molecular response within 3 months of therapy with tyrosine kinase inhibitors. *Cancer* 2021; **127:** 2648–56.

89 Ghobadi A, Slade M, Kantarjian H, et al. The role of allogeneic transplant for adult Ph+ ALL in CR1 with complete molecular remission: a retrospective analysis. *Blood* 2022; **140:** 2101–12.

90 Zeng Q, Xiang B, Liu Z. Comparison of allogeneic hematopoietic stem cell transplantation and TKI combined with chemotherapy for adult Philadelphia chromosome positive acute lymphoblastic leukemia: a systematic review and meta-analysis. *Cancer Med* 2021; **10:** 8741–53.

91 Huguet F, Leguay T, Raffoux E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J Clin Oncol* 2009; **27:** 911–18.

92 DeAngelo DJ, Stevenson KE, Dahlberg SE, et al. Long-term outcome of a pediatric-inspired regimen used for adults aged 18–50 years with newly diagnosed acute lymphoblastic leukemia. *Leukemia* 2015; **29:** 526–34.

93 Siegel SE, Stock W, Johnson RH, et al. Pediatric-inspired treatment regimens for adolescents and young adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: a review. *JAMA Oncol* 2018; **4:** 725–34.

94 Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood* 2019; **133:** 1548–59.

95 Rausch CR, Jabbour EJ, Kantarjian HM, Kadia TM. Optimizing the use of the hyperCVAD regimen: clinical vignettes and practical management. *Cancer* 2020; **126:** 1152–60.

96 Maury S, Chevret S, Thomas X, et al. Rituximab in B-lineage adult acute lymphoblastic leukemia. *N Engl J Med* 2016; **375:** 1044–53.

97 Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood* 2018; **131:** 1522–31.

98 Jabbour E, Short NJ, Jain N, et al. Hyper-CVAD and sequential blinatumomab for newly diagnosed Philadelphia chromosome-negative B-cell acute lymphocytic leukaemia: a single-arm, single-centre, phase 2 trial. *Lancet Haematol* 2022; **9:** e878–85.

99 Geyer MB, Hsu M, Devlin SM, Tallman MS, Douer D, Park JH. Overall survival among older US adults with ALL remains low despite modest improvement since 1980: SEER analysis. *Blood* 2017; **129:** 1878–81.

100 O'Brien S, Thomas DA, Ravandi F, Faderl S, Pierce S, Kantarjian H. Results of the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen in elderly patients with acute lymphocytic leukemia. *Cancer* 2008; **113:** 2097–101.

101 Li S, Molony JT, Chia V, Katz AJ. Patient characteristics and treatment patterns in elderly patients newly diagnosed with acute lymphoblastic leukemia (ALL) using 100% Medicare ALL data. *Blood* 2016; **128:** 3981.

102 Kantarjian H, Ravandi F, Short NJ, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study. *Lancet Oncol* 2018; **19:** 240–48.

103 Wieduwilt MJ, Yin J, Kour O, et al. Chemotherapy-free treatment with inotuzumab ozogamicin and blinatumomab for older adults with newly diagnosed, Ph-negative, CD22-positive, B-cell acute lymphoblastic leukemia: Alliance A041703. *J Clin Oncol* 2023; **41** (suppl)**:** 7006.

104 Jain N, Lamb AV, O'Brien 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:** 1863–69.

105 Coustan-Smith E, Mullighan CG, Onciu M, et al. Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia. *Lancet Oncol* 2009; **10:** 147–56.

106 Zhang J, Ding L, Holmfeldt L, et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. *Nature* 2012; **481:** 157–63.

107 Morita K, Jain N, Kantarjian H, et al. Outcome of T-cell acute lymphoblastic leukemia/lymphoma: focus on near-ETP phenotype and differential impact of nelarabine. *Am J Hematol* 2021; **96:** 589–98.

108 Short NJ, Jabbour E, Jain N, et al. A phase 1/2 study of mini-hyper-CVD plus venetoclax in patients with relapsed/refractory acute lymphoblastic leukemia. *Blood Adv* 2024; **8:** 909–15.

109 Luskin MR, Shimony S, Keating JH, et al. Venetoclax plus low intensity chemotherapy for adults with acute lymphoblastic leukemia. *Blood Adv* 2025; **9:** 617–26.

110 Zhang X, Yang J, Li J, et al. Analysis of 60 patients with relapsed or refractory T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma treated with CD7-targeted chimeric antigen receptor-T cell therapy. *Am J Hematol* 2023; **98:** 1898–908.

111 Lu P, Liu Y, Yang J, et al. Naturally selected CD7 CAR-T therapy without genetic manipulations for T-ALL/LBL: first-in-human phase 1 clinical trial. *Blood* 2022; **140:** 321–34.

112 Gomes-Silva D, Srinivasan M, Sharma S, et al. CD7-edited T cells expressing a CD7-specific CAR for the therapy of T-cell malignancies. *Blood* 2017; **130:** 285–96.

113 Roberts KG, Gu Z, Payne-Turner D, et al. High frequency and poor outcome of Philadelphia chromosome-like acute lymphoblastic leukemia in adults. *J Clin Oncol* 2017; **35:** 394–401.

114 Tanasi I, Ba I, Sirvent N, et al. Efficacy of tyrosine kinase inhibitors in Ph-like acute lymphoblastic leukemia harboring ABL-class rearrangements. *Blood* 2019; **134:** 1351–55.

115 Jabbour E, Patel K, Jain N, et al. Impact of Philadelphia chromosome-like alterations on efficacy and safety of blinatumomab in adults with relapsed/refractory acute lymphoblastic leukemia: a post hoc analysis from the phase 3 TOWER study. *Am J Hematol* 2021; **96:** E379–83.

116 Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med* 2014; **371:** 1005–15.

117 Senapati J, Jabbour E, Konopleva M, et al. Philadelphia-like genetic rearrangements in adults with B-cell ALL: refractoriness to chemotherapy and response to tyrosine kinase inhibitor in *ABL* class rearrangements. *JCO Precis Oncol* 2023; **7:** e2200707.

118 Pui C-H, Thiel E. Central nervous system disease in hematologic malignancies: historical perspective and practical applications. *Semin Oncol* 2009; **36** (suppl 2)**:** S2–16.

119 Kopmar NE, Cassaday RD. How I prevent and treat central nervous system disease in adults with acute lymphoblastic leukemia. *Blood* 2023; **141:** 1379–88.

120 Tang J, Yu J, Cai J, et al. Prognostic factors for CNS control in children with acute lymphoblastic leukemia treated without cranial irradiation. *Blood* 2021; **138:** 331–43.

121 Paul S, Kantarjian H, Sasaki K, et al. Intrathecal prophylaxis with 12 versus 8 administrations reduces the incidence of central nervous system relapse in patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia. *Am J Hematol* 2023; **98:** E11–14.

122 Jabbour E, Thomas D, Cortes J, Kantarjian HM, O'Brien S. Central nervous system prophylaxis in adults with acute lymphoblastic leukemia: current and emerging therapies. *Cancer* 2010; **116:** 2290–300.

123 Lazarus HM, Richards SM, Chopra R, et al. Central nervous system involvement in adult acute lymphoblastic leukemia at diagnosis: results from the international ALL trial MRC UKALL XII/ECOG E2993. *Blood* 2006; **108:** 465–72.

124 Orvain C, Chantepie S, Thomas X, et al. Impact of central nervous system involvement in adult patients with Philadelphia-negative acute lymphoblastic leukemia: a GRAALL-2005 study. *Haematologica* 2023; **108:** 3287–97.

125 Qi Y, Zhao M, Hu Y, et al. Efficacy and safety of CD19-specific CAR T cell-based therapy in B-cell acute lymphoblastic leukemia patients with CNSL. *Blood* 2022; **139:** 3376–86.

126 Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. *JAMA Oncol* 2017; **3:** e170580.

127 Saygin C, Cannova J, Stock W, Muffly L. Measurable residual disease in acute lymphoblastic leukemia: methods and clinical context in adult patients. *Haematologica* 2022; **107:** 2783–93.

128 Haddad FG, Jabbour E, Short NJ, Jain N, Kantarjian H. SOHO state of the art updates and next questions: update on the approach to Philadelphia chromosome-positive acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk* 2024; **24:** 271–76.

129 Jabbour EJ, Short NJ, Jain N, et al. Blinatumomab is associated with favorable outcomes in patients with B-cell lineage acute lymphoblastic leukemia and positive measurable residual disease at a threshold of 10^{-4} and higher. *Am J Hematol* 2022; **97:** 1135–41.

130 Shah BD, Cassaday RD, Park JH, et al. Three-year analysis of adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia treated with brexucabtagene autoleucel in ZUMA-3. *Leukemia* 2025; **39:** 1058–68.

131 Jabbour E, Ravandi F, Kebriaei P, et al. Salvage chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD for patients with relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukemia: a phase 2 clinical trial. *JAMA Oncol* 2018; **4:** 230–34.

132 Kantarjian H, Haddad FG, Jain N, et al. Results of salvage therapy with mini-hyper-CVD and inotuzumab ozogamicin with or without blinatumomab in pre-B acute lymphoblastic leukemia. *J Hematol Oncol* 2023; **16:** 44.

133 Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. *Lancet Oncol* 2012; **13:** 403–11.

134 Kantarjian H, Thomas D, Jorgensen J, et al. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. *Cancer* 2013; **119:** 2728–36.

135 Jabbour E, Short N, Jain N, et al. ALL-808 very promising results of the dose dense (D-D) mini-hyper-CVD-inotuzumab-blinatumomab phase 2 trial in patients with relapsed-refractory acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk* 2024; **24:** S284–85.

136 Jabbour E, Lussana F, Martínez-Sánchez P, et al. Subcutaneous blinatumomab in adults with relapsed or refractory B-cell acute lymphoblastic leukaemia: post-hoc safety and activity analysis from a multicentre, single-arm, phase 1/2 trial. *Lancet Haematol* 2025; **12:** e529–41.

137 Pasvolsky O, Kebriaei P, Shah BD, Jabbour E, Jain N. Chimeric antigen receptor T-cell therapy for adult B-cell acute lymphoblastic leukemia: state-of-the-(C)ART and the road ahead. *Blood Adv* 2023; **7:** 3350–60.

138 Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med* 2018; **378:** 449–59.

139 Roddie C, Sandhu KS, Tholouli E, et al. Obecabtagene autoleucel in adults with B-cell acute lymphoblastic leukemia. *N Engl J Med* 2024; **391:** 2219–30.

140 Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med* 2018; **378:** 439–48.

141 Xu X, Sun Q, Liang X, et al. Mechanisms of relapse after CD19 CAR T-cell therapy for acute lymphoblastic leukemia and its prevention and treatment strategies. *Front Immunol* 2019; **10:** 2664.

142 Ghorashian S, Lucchini G, Richardson R, et al. CD19/CD22 targeting with cotransduced CAR T cells to prevent antigen-negative relapse after CAR T-cell therapy for B-cell ALL. *Blood* 2024; **143:** 118–23.

143 Schultz LM, Baggott C, Prabhu S, et al. Disease burden impacts outcomes in pediatric and young adult B-cell acute lymphoblastic leukemia after commercial tisagenlecleucel: results from the Pediatric Real World CAR Consortium (PRWCC). *Blood* 2020; **136** (suppl 1)**:** 14–15.

144 Roloff GW, Aldoss I, Kopmar NE, et al. Outcomes after brexucabtagene autoleucel administered as a standard therapy for adults with relapsed/refractory B-cell ALL. *J Clin Oncol* 2025; **43:** 558–566.