

Pediatric Acute Lymphoblastic Leukemia, Version 2.2020

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. Advancements in technology that enhance our understanding of the biology of the disease, risk-adapted therapy, and enhanced supportive care have contributed to improved survival rates. However, additional clinical management is needed to improve outcomes for patients classified as high risk at presentation (eg, T-ALL, infant ALL) and who experience relapse. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for pediatric ALL provide recommendations on the workup, diagnostic evaluation, and treatment of the disease, including guidance on supportive care, hematopoietic stem cell transplantation, and pharmacogenomics. This portion of the NCCN Guidelines focuses on the frontline and relapsed/refractory management of pediatric ALL.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

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All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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The complete NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Individual disclosures for the NCCN Pediatric Acute Lymphoblastic Leukemia Panel members can be found on page 112. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

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DIAGNOSIS

The diagnosis of ALL generally requires demonstration of $\geq 20\%$ bone marrow lymphoblasts^{e,f,g} upon hematopathology review of bone marrow aspirate and biopsy materials, which includes:

- Morphologic assessment of Wright-Giemsa-stained bone marrow aspirate smears, and H&E-stained core biopsy and clot sections
- Comprehensive flow cytometric immunophenotyping^h
- Baseline characterization of leukemic clone to facilitate subsequent minimal residual disease (MRD) analysisⁱ

GENETIC CHARACTERIZATION

Optimal risk stratification and treatment planning require testing marrow or peripheral blood lymphoblasts for specific recurrent genetic abnormalities using:

- Karyotyping of G-banded metaphase chromosomes
- Interphase fluorescence in situ hybridization (FISH) testing, including probes capable of detecting the major recurrent genetic abnormalities^b
- Reverse transcriptase-polymerase chain reaction (RT-PCR) testing *BCR-ABL1* in B-ALL (quantitative or qualitative) including determination of transcript size (ie, p190 vs. p210)
 - If *BCR-ABL1* negative: encourage testing for gene fusions and mutations associated with *BCR-ABL1*-like (Ph-like) ALL^j

Additional optional tests include:

- Additional assessment (eg, microarray CGH) in cases of aneuploidy or failed karyotype
- Assessment of various potentially actionable or prognostic mutations (see Genetic Risk Groups [PEDALL-A^k])

CLASSIFICATION

- Together, these studies allow determination of the World Health Organization (WHO) ALL subtypes and genetic risk group^k
- [Patients should undergo evaluation and treatment at specialized centers](#)

Pediatric acute lymphoblastic leukemia (ALL)^{b,c,d}

→ See Workup (PEDALL-2)

*Available online, in these guidelines, at NCCN.org.

See Footnotes on PEDALL-1A

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PEDALL-1

Overview

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. The age-adjusted incidence rate of ALL in the United States is 1.38 per 100,000 individuals per year,¹ with approximately 5,930 new cases and 1,500 deaths estimated in 2019.² It is also the most common pediatric malignancy, representing 75%–80% of acute leukemias among children.³ The median age at diagnosis for ALL is 15 years,⁴ with 55.4% of patients diagnosed at younger than 20 years of age.⁵ In contrast, 28% of patients are diagnosed at 45 years or older and only approximately 12.3% of patients are diagnosed at 65 years or older.⁵

The cure rates and survival outcomes for pediatric patients with ALL have improved dramatically over the past several decades.⁶ Improvements are largely due to advances in the understanding of the molecular genetics and pathogenesis of the disease, the incorporation of risk-adapted therapy, the advent of new targeted agents, and the use of allogeneic hematopoietic stem cell transplantation (HSCT). Analyses from the SEER database have shown improvements in survival for children and adolescent and young adult (AYA) patients, with 5-year overall

survival (OS) rates of 89% and 61%, respectively.^{6,7} Although the exact OS percentage can vary based on how the age range is defined for pediatric, AYA, and adult patients, the trend is nonetheless clear that OS decreases substantially with increased age.⁸ The exception is infants younger than age 1. This age group has not seen any improvement in survival over the past 30 years, with a 6-year OS rate of 58.2%.⁹

AYA patients represent a unique population because they may receive treatment based on either a pediatric or an adult protocol, depending on local referral patterns and institutional practices. The NCCN Panel considers the term *pediatric* to include any patient aged 18 years or younger and certain AYA patients older than 18 years of age. These NCCN Guidelines are intended to apply to AYA patients treated in a pediatric oncology setting and may include patients up to age 30 years. The NCCN Guidelines for ALL are intended to apply to AYA patients treated in an adult oncology setting.

The NCCN Guidelines for Pediatric ALL were developed as a result of meetings convened by a multidisciplinary panel of pediatric ALL experts, with the goal of providing recommendations on standard treatment approaches based on current evidence. The NCCN Guidelines focus on risk assessment and stratification of

FOOTNOTES

^aThe pediatric ALL panel considers “pediatric” to include any patient aged 18 years and younger, and certain adolescent and young adult (AYA) patients older than 18 years of age. Practice patterns vary with regard to AYA patients from center to center in terms of whether ALL patients are treated primarily by pediatric or adult oncologists. This guideline is intended to apply to AYA patients treated in a pediatric oncology setting, and this may include patients up to age 30 years. The NCCN Guidelines for Acute Lymphoblastic Leukemia[†] are intended to apply to AYA patients treated in an adult oncology setting.

^bSubtypes: B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities includes hypodiploidy, hyperdiploidy, and commonly occurring translocations: t(9;22)(q34.1;q11.2)[BCR-ABL 1]; t(v;11q23.3)[KMT2A rearranged]; t(12;21)(p13.2;q22.1)[ETV6-RUNX1] dual-color probe set to detect cryptic t(12;21), which will also allow detection of iAMP21 (when ≥5 copies of the RUNX1 gene are detected); t(1;19)(q23;p13.3)[TCF3-PBX1]; t(5;14)(q31.1;q32.3)[IL3/IGH]; B-cell lymphoblastic leukemia/lymphoma, not otherwise specified; B-lymphoblastic leukemia/lymphoma, BCR-ABL 1-like; B-lymphoblastic leukemia/lymphoma with iAMP21; and early T-cell precursor (ETP) lymphoblastic leukemia. Additional FISH probes that may be useful include: centromeric probes for chromosomes 4, 10, and 17 to detect hyperdiploidy; CDKN2A at 9p21.3 to detect deletions; probes to detect cryptic t(X;14)(p22;q32)/t(Y;14)(p11;q32) IGH-CRLF2 rearrangements; and probes to detect cryptic JAK2 and FGFR1 rearrangements.

^cCriteria for classification of mixed phenotype acute leukemia (MPAL) should be based on the WHO 2016 criteria. Note that in ALL, myeloid-associated antigens such as CD13 and CD33 may be expressed, and the presence of these myeloid markers does not exclude the diagnosis of ALL, nor is it associated with adverse prognosis.

^dBurkitt leukemia/lymphoma; see the NCCN Guidelines for B-Cell Lymphomas[†].

^eWhile these guidelines pertain primarily to patients with leukemia, patients with lymphoblastic lymphoma (LL) (B- or T-cell) would likely also benefit from ALL-like regimens. Such patients should be treated in a center that has experience with LL.

^fIf there are sufficient numbers of circulating lymphoblasts (at least 1,000 per microliter as a general guideline) and clinical situation precludes bone marrow aspirate and biopsy, then peripheral blood can be substituted for bone marrow.

^gIn many treatment protocols, a value of >25% marrow blasts is used to define leukemia. Unlike with myeloid leukemias, there is no agreed-upon lower limit for the proportion of blasts required to establish a diagnosis of ALL. In general, the diagnosis should be avoided when there are <20% blasts. Presentations of ALL with low blast counts are uncommon; there is no compelling evidence that failure to treat a patient when there are <20% marrow lymphoblasts has an adverse effect on outcome. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. IARC Press: Lyon 2017.

^hThe following immunophenotypic findings are particularly notable: CD10 negativity correlates with KMT2A rearrangement (KMT2Ar); ETP T-ALL (lacking expression of CD5, CD8, and CD1a and expression of one or more myeloid/stem cell markers); CD20 positivity: definition not clear, most studies have used >20% of blasts expressing CD20. CRLF2 overexpression as a surrogate for genomic alterations of the CRLF2 gene (Harvey RC, Wood BL, Chem IM, et al. Identification of CRLF2 genetic lesions in patients with pediatric B-precursor acute lymphoblastic leukemia [BCP ALL] by flow cytometry or quantitative RT-PCR: A Children’s Oncology Group [COG] Study. Blood 2012;120:2529). Flow cytometric DNA ploidy analysis could be considered for rapid identification of hyperdiploid and hypodiploid B-ALL.

ⁱBy either flow cytometric analysis or by identification of clonal immunoglobulin or T-cell receptor gene rearrangements.

^jThe BCR-ABL 1-like (Ph-like) phenotype is associated with recurrent gene fusions and mutations that activate tyrosine kinase pathways and includes gene fusions involving ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK2, or PDGFRB and mutations involving CRLF2, FLT3, IL7R, SH2B3, JAK1, JAK3, and JAK2 (in combination with CRLF2 gene fusions). Testing for these abnormalities at diagnosis may aid in risk stratification. Low-density array (LDA) (Harvey RC, Kang H, Roberts KG, et al. Blood 2013;122:21), next-generation sequencing (NGS)-based assays, and multiplex RT-PCR are used to detect a signature or cryptic rearrangements and mutations characteristic of BCR-ABL 1-like ALL. The safety and efficacy of targeted agents in this population is an area of active research.

^kSee Genetic Risk Groups for B-ALL (PEDALL-A*).

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PEDALL-1A

risk-adapted therapy; treatment strategies for Philadelphia chromosome (Ph)-positive and Ph-negative B-cell lineage (B-ALL), T-cell lineage (T-ALL), and infant ALL; and supportive care considerations. Given the complexity of ALL treatment regimens and the required supportive care measures, the NCCN Pediatric ALL Panel recommends that patients be treated at a specialized cancer center with expertise in the management of ALL. This portion of the NCCN Guidelines discusses recommendations for the diagnosis and workup of pediatric ALL and focuses on frontline and relapsed/refractory (R/R) management strategies for B-ALL, T-ALL, and infants with ALL. For the complete and most updated version of these guidelines, visit NCCN.org.

Diagnosis

Clinical Presentation

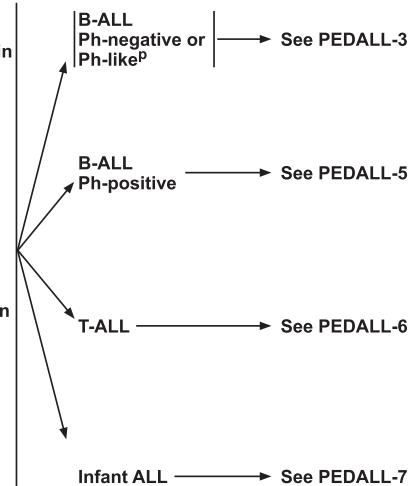
Patients with ALL develop symptoms related to the infiltration of blasts in the bone marrow, lymphoid system, and extramedullary sites (including the central nervous system [CNS] and testicles).³ These symptoms may include fatigue or lethargy, constitutional symptoms (eg, fevers, night sweats, weight loss), dyspnea, dizziness, infections, and easy bruising or bleeding.^{10,11} Chin numbness or

facial palsy may result from cranial nerve or CNS involvement.^{12,13} Among children, pain in the extremities or joints may be the only presenting symptom.¹¹ The presence of lymphadenopathy, splenomegaly, and/or hepatomegaly on physical examination may be found in approximately 20% of patients. Abdominal masses from gastrointestinal involvement are more suggestive of mature B-cell ALL (Burkitt lymphoma).¹¹

The diagnosis of ALL generally requires demonstration of ≥20% bone marrow lymphoblasts on hematopathology review of bone marrow aspirate and biopsy materials (see PEDALL-1, page 82). A value of >25% marrow blasts is often used in treatment protocols to define leukemia.¹⁴ Unlike with myeloid leukemia, there is no clear lower limit for the proportion of blasts required to establish an ALL diagnosis. In general, presentations of ALL with low blast counts are uncommon, and the diagnosis of ALL should be avoided when there are <20% marrow blasts.¹⁴ In addition, no compelling evidence exists that failure to treat a patient with <20% marrow blasts has an adverse effect on outcome.¹⁴ Peripheral blood may be substituted for bone marrow provided there is a significant amount of circulating disease,^{15,16} with the NCCN Pediatric ALL Panel suggesting a general guide of ≥1,000 circulating lymphoblasts per microliter or ≥20% lymphoblasts.

WORKUP¹

- History and physical (H&P)
- Complete blood count (CBC), differential, chemistry profile, liver function tests (LFTs)
- Tumor lysis syndrome (TLS) panel: LDH, uric acid, K, Ca, Phos (See Tumor Lysis Syndrome in Principles of Supportive Care [PEDALL-B*])
- Disseminated intravascular coagulation (DIC) panel: d-dimer, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT)
- Pregnancy testing, fertility counseling, and preservation as indicated
- CT/MRI of head with contrast, if neurologic symptoms
- Chest x-ray to rule out mediastinal mass
- Whole body PET/CT if lymphoblastic lymphoma suspected
- Lumbar puncture (LP)^{m,n} with IT chemotherapy
 - See Evaluation and Treatment of Extramedullary Involvement (PEDALL-C*)
- Testicular exam, including scrotal ultrasound as indicated
- Infection evaluation:
 - Screen for opportunistic infections, as appropriate
- Assessment of left ventricular function (echocardiogram or cardiac nuclear medicine scan) in all patients, who will receive anthracyclines as part of treatment plan.
- Central venous access device of choice
- Consider pharmacogenomic testing for *TPMT*, *NUDT15* (see Pharmacogenomics [PEDALL-G*])
- Consider predisposition syndromes
 - Down syndrome is an important ALL predisposition syndrome.
 - For non-Down syndrome-related ALL the majority of patients do not have an identifiable leukemia predisposition syndrome. One important exception is hypodiploid ALL where germline *TP53* mutations are common and testing should be considered.
 - Other germline mutations associated with ALL risk have been reported.^o



¹ The following list represents minimal recommendations; other testing may be warranted according to clinical symptoms and discretion of the clinician.

^m For patients with major neurologic signs or symptoms at diagnosis, appropriate imaging studies should be performed to detect meningeal disease, chloromas, or central nervous system (CNS) bleeding. See Evaluation and Treatment of Extramedullary Involvement (PEDALL-C*).

ⁿ Timing of LP should be consistent with the chosen treatment regimen. Pediatric-inspired regimens typically include LP and prophylactic IT chemotherapy at the time of diagnostic workup. The panel recommends that LP be done concurrently with initial IT therapy.

^o Pui CH, Nichols KE, Yang JJ. Somatic and germline genomics in paediatric acute lymphoblastic leukaemia. Nat Rev Clin Oncol 2019;16:227-240.

^p Ph-like ALL is classified using LDA, FISH, RT-PCR, and NGS (Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesion in Ph-like acute lymphoblastic leukemia. N Engl J Med 2014;37:1005-1015).

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PEDALL-2

The 2016 WHO classification lists ALL and lymphoblastic lymphoma as the same entity, distinguished only by the primary location of the disease.^{14,17} When the disease is restricted to a mass lesion primarily involving nodal or extranodal sites with no or minimal involvement in blood or bone marrow (generally defined as <20% lymphoblasts in the marrow), the case would be consistent with a diagnosis of lymphoblastic lymphoma.^{14,17} However, based on morphologic, genetic, and immunophenotypic features, lymphoblastic lymphoma is indistinguishable from ALL. Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens versus traditional lymphoma therapy^{18,19} and should be treated in a center that has experience with lymphoblastic lymphoma.

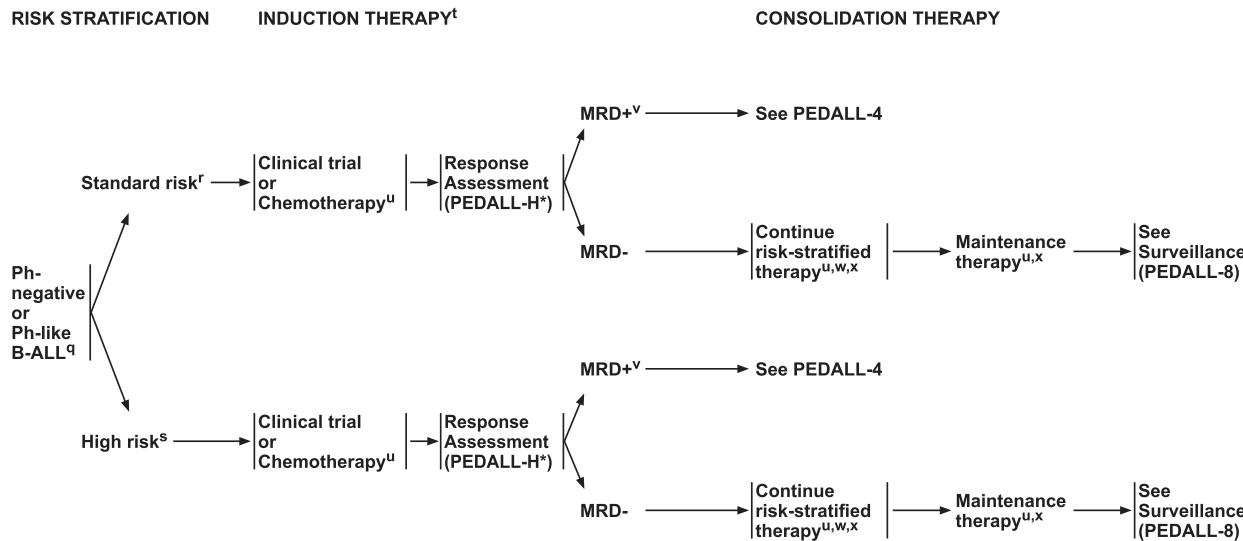
Hematopathology evaluations should include morphologic examination of malignant lymphocytes using Wright-Giemsa-stained slides and hematoxylin and eosin-stained core biopsy and clot sections; comprehensive immunophenotyping with flow cytometry (see the full version of the discussion section in these guidelines for more details on immunophenotyping); and baseline characterization of leukemic clone(s)—by flow cytometry, or identification of clonal immunoglobulin or T-cell receptor gene rearrangements—to

facilitate subsequent analysis of minimal residual disease (MRD).

Genetic Abnormalities and Molecular Subtypes

Identification of specific recurrent genetic abnormalities is critical for disease evaluation, optimal risk stratification, and treatment planning. Subtypes of B-ALL with recurrent genetic abnormalities include the following: hyperdiploidy (51–67 chromosomes); hypodiploidy (<44 chromosomes); t(9;22)(q34.1;q11.2), *BCR-ABL1*; t(v;11q23.3), *KMT2A rearranged*; t(12;21)(p13.2;q22.1), *ETV6-RUNX1*; t(1;19)(q23;p13.3), *TCF3-PBX1*; and t(5;14)(q31.1;q32.1), *IL3-IGH*.²⁰ During the 2016 WHO classification update, 2 new provisional entities were added to the B-ALL classification: B-lymphoblastic leukemia/lymphoma with translocations involving tyrosine kinases or cytokine receptors (*BCR-ABL1*-like ALL or Ph-like ALL)^{21,22} and B-lymphoblastic leukemia/lymphoma with intrachromosomal amplification of chromosome 21 (*iAMP21*).^{21,23} Two new provisional entities were also added to T-ALL: early T-cell precursor lymphoblastic leukemia and natural killer cell lymphoblastic leukemia/lymphoma.²¹

In these guidelines, the NCCN Panel for Pediatric ALL has delineated the features that are commonly associated



^qFor patients with Down syndrome, see Special Considerations for Vulnerable Populations (PEDALL-D*).

^r Standard risk criteria are consistent with NCI: WBC <50,000/mm³, ≥1 y to <10 y. For further details see the Risk Stratification Definitions (PEDALL-E*).

^s High-risk criteria are consistent with NCI: WBC ≥50,000/mm³, <1 y to ≥10 y. For further details see the Risk Stratification Definitions (PEDALL-E*).

^t See Principles of Supportive Care (PEDALL-B*).

^u See Principles of Systemic Therapy (PEDALL-F*).

^v The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information see Minimal Residual Disease (PEDALL-I*).

^w See Risk Stratification Definitions for Post-Induction Therapy (PEDALL-E, 2 of 3*).

^x For Ph-like patients, TKIs may be considered. For more information see Principles of Systemic Therapy (PEDALL-F*).

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PEDALL-3

with favorable or unfavorable outcomes in B-ALL (see “Genetic Risk Groups for B-ALL,” available in these guidelines at NCCN.org). A brief summary is also provided in this discussion for genetic features associated with T-ALL.

Favorable Risk Features

Among children with ALL, the most common chromosomal abnormality is hyperdiploidy (>50 chromosomes) as seen in 25% of cases of B-ALL compared with 7% in the adult ALL patient population.^{24,25} The *ETV6-RUNX1* subtype (also within the B-cell lineage) resulting from chromosomal translocation t(12;21) is also among the most commonly occurring subtypes in childhood ALL (25%) compared with adults (2%).^{24,25} Both hyperdiploidy and *ETV6-RUNX1* subtypes are associated with favorable outcomes in pediatric ALL,²⁶ and occur less frequently among AYA patients compared with younger children.²⁴

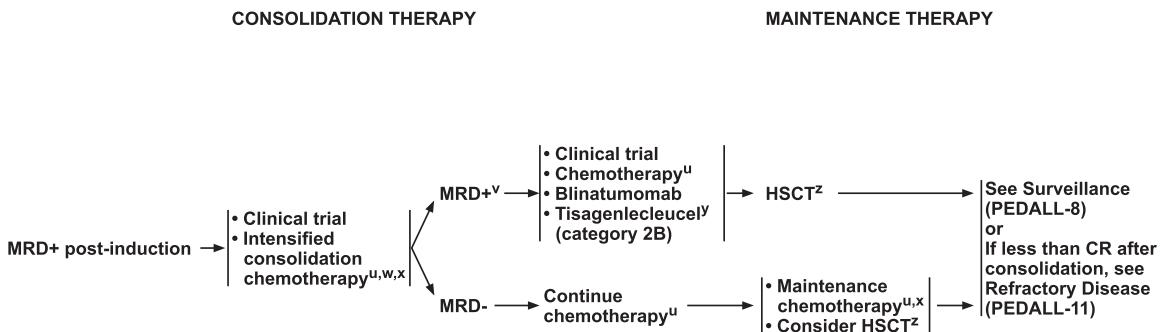
Unfavorable Risk Features

Several chromosomal abnormalities are well-recognized prognostic biomarkers of high-risk disease at all ages, including low hypodiploidy (30–39 chromosomes), near haploidy (<30 chromosomes), *KMT2A* (*MLL*) translocations, t(17;19)/*TCF3-HLF* fusion, and *BCR-ABL1*.²⁷

Hypodiploidy is associated with poor prognosis and is observed in 1%–2% of pediatric patients.^{28–30} Of note, low hypodiploidy is associated with a high frequency of *TP53* alterations, which are germline in ~50% of cases.^{31,32}

Chromosomal rearrangements involving the *KMT2A* gene, previously referred to as the human mixed lineage leukemia (MLL) gene, occur in approximately 5% of pediatric ALL cases, with a higher incidence in infants (~70%–80%).^{33–36} These *KMT2A* rearrangements, including cases with t(4;11) translocation, are associated with poor outcomes, especially in infants.^{37,38} The translocation t(17;19)(q22;p13), resulting in the fusion gene *TCF3-HLF*, defines a rare subtype of pediatric ALL (<1%) and is associated with poor outcomes.^{39,40} Conversely, another translocation t(1;19) that results in the fusion gene *TCF3-PBX1* occurs in approximately 5% of pediatric ALL cases and is associated with intermediate outcomes.^{39,41}

B-ALL with *iAMP21* is characterized by amplification of a portion of chromosome 21, detected by fluorescence in situ hybridization (FISH) with a probe for the *RUNX1* gene.^{42,43} Occurring in approximately 2% of children with ALL, B-ALL with *iAMP21* is associated with adverse prognosis when treated with low-intensity regimens.^{42,43} Children with *iAMP21* are typically older, with a median



^uSee Principles of Systemic Therapy (PEDALL-F*).

^vThe threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information see Minimal Residual Disease (PEDALL-1*).

^wSee Risk Stratification Definitions for Post-Induction Therapy (PEDALL-E, 2 of 3*).

^xFor Ph-like patients, TKIs may be considered. For more information see Principles of Systemic Therapy (PEDALL-F*).

^yThe use of tisagenlecleucel in this setting is strongly recommended in the context of a clinical trial. See Tisagenlecleucel section in the Principles of Systemic Therapy (PEDALL-F [10 of 12]*).

^zSee Principles of Hematopoietic Stem Cell Transplant (PEDALL-J*).

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PEDALL-4

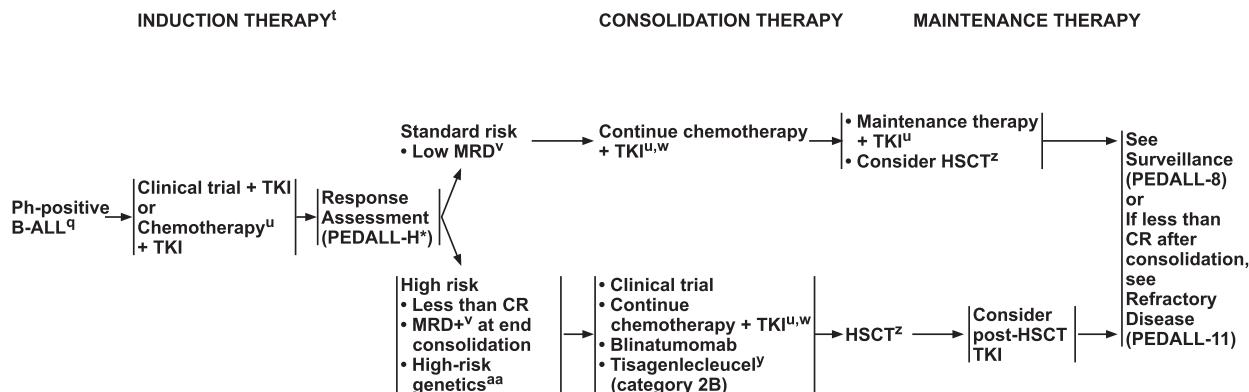
age of 9 years, and have low platelet counts and low white blood cell (WBC) counts.⁴⁴

BCR-ABL1- or Ph-positive ALL is associated with poor prognosis and is relatively uncommon among childhood ALL (2%), whereas this subtype is more common among adults (25%).^{24,25} The frequency of Ph-positive ALL increases with age, and younger children (1–9 years) with Ph-positive ALL have a better prognosis than adolescents with this subtype.^{45,46}

In B-ALL, mutations in the Ikaros gene (*IKZF1*) are seen in approximately 15%–20% of patients with pediatric B-ALL^{47,48} and at a higher frequency of >75% in patients who are also *BCR-ABL1* positive.^{47,49} In many studies, *IKZF1* mutations are associated with a poor prognosis and a greater incidence of relapse.^{49,50} An analysis of the MRD-dependent prognostic impact of *IKZF1* deletions with co-occurring deletions in *CDKN2A*, *CDKN2B*, *PAX5*, or *PARI* in the absence of *ERG* deletion conferred poor outcomes in pediatric patients with B-ALL.⁵¹ Emerging data suggests that an intragenic *ERG* deletion is associated with favorable outcomes in pediatric B-ALL, and in this context, co-occurring *IKZF1* deletions do not affect prognosis.^{52,53}

BCR-ABL1-like or Ph-like ALL is a subgroup of B-ALL associated with unfavorable prognosis that occurs in

approximately 15% of pediatric patients with ALL.^{22,54,55} A study using gene expression signatures to classify pediatric patients with ALL into subtypes estimated the 5-year disease-free survival (DFS) in the *BCR-ABL1*-like ALL group to be 60%.²² In adult patients with *BCR-ABL1*-like ALL, the 5-year event-free survival (EFS) is significantly lower (22.5%; 95% CI, 14.9%–29.3%) compared with patients with non-*BCR-ABL1*-like ALL (49.3%; 95% CI, 42.8%–56.2%).⁵⁶ Although this subgroup is Ph-negative, they show an otherwise similar genetic profile to the Ph-positive ALL subgroup, including an *IKZF1* mutation.⁴⁹ A study evaluating the relationship between *BCR-ABL1*-like and *IKZF1* in children with B-cell precursor ALL showed that 40% of cases had co-occurrence of these mutations.⁵⁷ The presence of the *BCR-ABL1*-like signature and an *IKZF1* deletion were indicative of poor prognosis independent of conventional risk factors.⁵⁷ Genomically, the Ph-like subtype is typically associated with gene fusions and mutations that activate tyrosine kinase pathways as the common mechanism of transformation. These gene fusions and mutations include ABL-class rearrangements (ie, *ABL1*, *ABL2*, *PDGFRA*, *PDGFRβ*, *FGFR*), JAK-STAT rearrangements and/or mutations (ie, *CRLF2*,⁵⁸ *EPOR*, *JAK1*, *JAK2*, *JAK3*, *TYK2*, *SH2B3*, *IL7R*) and other rearrangements in *FLT3*, *NTRK3*, *LYN*,



^qFor patients with Down syndrome, see Special Considerations for Vulnerable Populations (PEDALL-D*).

^t See Principles of Supportive Care (PEDALL-B*).

^u See Principles of Systemic Therapy (PEDALL-F*).

^v The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information see Minimal Residual Disease (PEDALL-I*).

^w See Risk Stratification Definitions for Post-Induction Therapy (PEDALL-E, 2 of 3*).

^y The use of tisagenlecleucel in this setting is strongly recommended in the context of a clinical trial. See Tisagenlecleucel section in the Principles of Systemic Therapy (PEDALL-F [10 of 12]*).

^z See Principles of Hematopoietic Stem Cell Transplant (PEDALL-J*).

^{aa} eg, KMT2Ar, low hypodiploidy, TCF3-PBX1, IKZF1 deletion may be considered as a high-risk feature but is not universally accepted as a high-risk feature for which therapy is changed.

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and, *PTK2B* genes.^{22,59,60} Genomic profiling studies have found that at least 80% of Ph-like ALL cases have cytokine receptor- or kinase-activating alterations, suggesting potential for *ABL*-class tyrosine kinase inhibitors (TKIs) or JAK small molecule inhibitors to significantly improve patient outcomes in this subgroup.^{59–61}

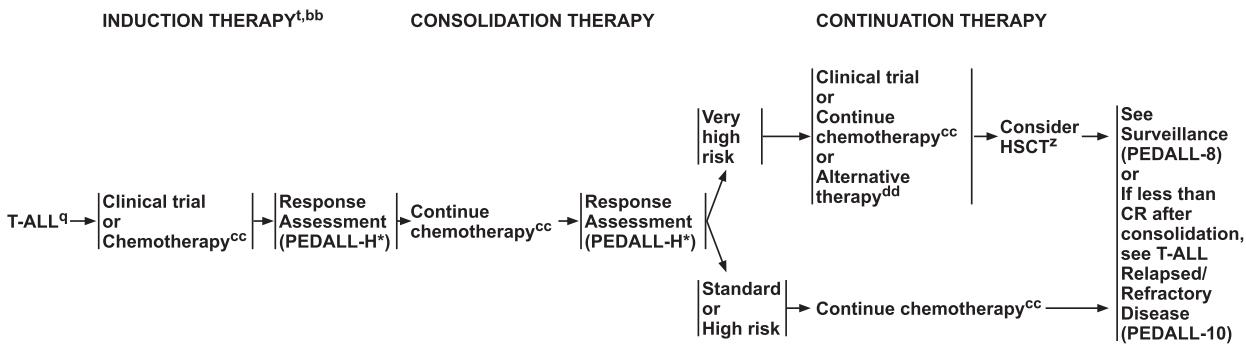
Genetic Abnormalities Associated With T-ALL

T-ALL is characterized by activating mutations of *NOTCH1*, and rearrangements of transcription factors *TLX1* (*HOX11*), *TLX3* (*HOX11L2*), *LYL1*, *TAL1*, and *KMT2A*.^{55,62} More than 50% of T-ALL cases have activating *NOTCH1* mutations, and approximately 10%–15% of T-ALL cases have mutations in the *NOTCH1*-targeting E3 ligase *FBXW7*, which leads to prolonged *NOTCH1* activation.^{63–65} In patients with T-ALL, *NOTCH1* and *FBXW7* mutations have generally been associated with favorable prognosis and lower MRD levels.^{66–68} However, it is unclear if these mutations are independent predictors of outcome, or if there needs to be concurrent absence of *RAS* or *PTEN* mutations.^{69–71}

NCCN Recommendations for Genetic Characterization

The presence of recurrent genetic abnormalities should be evaluated using karyotyping of G-banded metaphase

chromosomes (conventional cytogenetics), interphase FISH assays, and reverse transcription-polymerase chain reaction (RT-PCR) testing (see PEDALL-1, page 82). FISH probes and RT-PCR primers should include those capable of detecting major recurrent genetic abnormalities. RT-PCR should measure transcript sizes (ie, p190 vs p210) of *BCR-ABL1* in B-ALL. If samples are *ETV6-RUNX1*- and *BCR-ABL1*-negative, testing for other gene fusions and mutations associated with Ph-like ALL is encouraged in some patients, and may aid in risk stratification. Recurrent gene fusions and mutations that activate tyrosine kinase pathways and are associated with Ph-like ALL include gene fusions involving *ABL1*, *ABL2*, *CRLF2*, *CSF1R*, *EPOR*, *JAK2*, or *PDGFRB* (gene fusions) and mutations involving *CRLF2*, *FLT3*, *IL7R*, *SH2B3*, *JAK1*, *JAK3*, and *JAK2* (in combination with *CRLF2* gene fusions).^{60,72} Low-density arrays,⁷³ next-generation sequencing (NGS)-based assays, and multiplex RT-PCR are typically used to detect signature or cryptic rearrangements and mutations characteristic of Ph-like ALL. Additional FISH probes that may be useful to consider include centromeric probes for chromosomes 4, 10, and 17 to detect hyperdiploidy; *CDKN2A* at 9p21.3 to detect deletions; probes to detect cryptic t(X;14)(p22;q32)/t(Y;14)(p11;q32) IGH-CRLF2 rearrangements; and probes to detect cryptic *JAK2* and

**T-ALL Post-Induction Risk Group Definitions:**

Risk Group	Features ^v
Very High	End consolidation MRD >0.1%
High	Absence of standard and very high features
Standard	Day 29 MRD <0.01% and CNS-1 and absence of testicular disease and no steroid pretreatment ^{ee}

^qFor patients with Down syndrome, see Special Considerations for Vulnerable Populations (PEDALL-D*).

^t See Principles of Supportive Care (PEDALL-B*).

^v The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information see Minimal Residual Disease (PEDALL-I*).

^z See Principles of Hematopoietic Stem Cell Transplant (PEDALL-J*).

^{bb} MRD and morphologic marrow response should be assessed after induction, and if not MRD negative, repeat assessment after consolidation therapy. Assess MRD at additional time points based on chemotherapy regimen and response as indicated. See Minimal Residual Disease (PEDALL-I*).

^{cc} See regimens for T-ALL on Principles of Systemic Therapy (PEDALL-F, 2 of 12*).

^{dd} See regimens for T-ALL on Principles of Systemic Therapy (PEDALL-F, 9 of 12*).

^{ee} The specific definition of steroid pretreatment differs by protocol. Refer to regimen-specific definition of steroid pretreatment.

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PEDALL-6

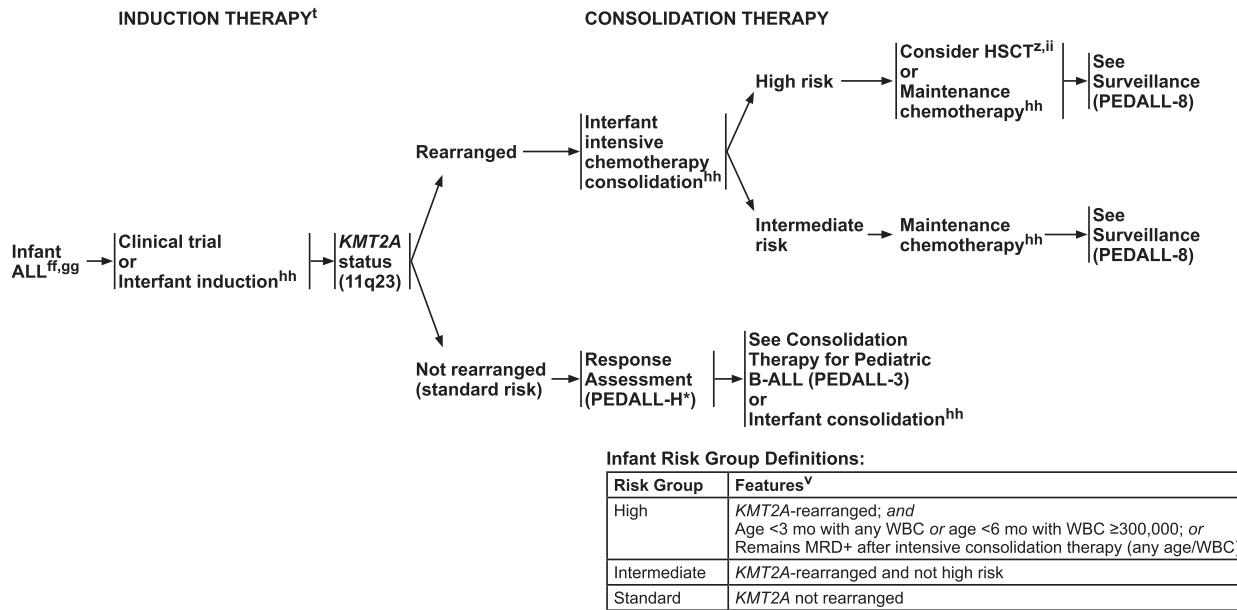
FGFR1 rearrangements.⁷⁴ In cases of aneuploidy or failed karyotype, additional assessment may include a microarray comparative genomic hybridization.

Workup

The initial workup for patients with ALL should include a thorough medical history and physical examination along with laboratory and imaging studies, where applicable (See PEDALL-2, page 84). Laboratory studies include a complete blood count (CBC) with platelets and differential, a blood chemistry profile, liver function tests, and disseminated intravascular coagulation panel (including measurements for D-dimer, fibrinogen, prothrombin time, and partial thromboplastin time). The blood chemistry panel should include a tumor lysis syndrome panel (including measurements for serum lactate dehydrogenase, uric acid, potassium, phosphates, and calcium). Female patients should undergo pregnancy testing and all male patients should be evaluated for testicular involvement of disease, including a scrotal ultrasound as indicated; testicular involvement is rare in ALL (1%-2% of males), but is slightly more common in T-ALL than B-ALL. Fertility counseling and/or preservation options should be presented to all patients.

Appropriate imaging studies should also be performed to detect meningeal disease, chloromas, or CNS bleeding for patients with major neurologic signs or symptoms at diagnosis. If neurologic symptoms are observed, a CT/MRI scan of the head with contrast is recommended. To rule out mediastinal masses, a chest X-ray is recommended. If lymphoblastic lymphoma is suspected, a whole body PET/CT scan is recommended. CNS involvement should be evaluated through lumbar puncture at timing that is consistent with the treatment protocol. Pediatric-inspired regimens typically include lumbar puncture and prophylactic intrathecal chemotherapy at the time of diagnostic workup. The NCCN Pediatric ALL Panel recommends that the first intrathecal therapy be performed at initial scheduled lumbar puncture unless directed by symptoms to perform earlier (see full version of these guidelines for "NCCN Recommendations for Evaluation and Treatment of Extramedullary Involvement," available online at NCCN.org).

All patients should be evaluated for opportunistic infections as appropriate. In addition, an echocardiogram or cardiac scan should be considered for all patients due to the use of anthracyclines as the backbone of nearly all treatment regimens. Assessment of cardiac function is particularly important for patients with prior cardiac



^t See Principles of Supportive Care (PEDALL-B*).

^v The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information see Minimal Residual Disease (PEDALL-I*).

^z See Principles of Hematopoietic Stem Cell Transplant (PEDALL-J*).

^{ff} See Special Considerations for Vulnerable Populations (PEDALL-D*).

^{gg} Reproduced with permission: Brown P, Pieters R, Biondi A. How I treat infant leukemia. Blood 2019;133:205-214.

^{hh} See Principles of Systemic Therapy for Infant ALL (PEDALL-F, 2 of 12*).

ⁱⁱ If donor available, prefer non-total body irradiation-based prep regimen and age ≥6 mo at time of HSCT.

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history, prior anthracycline exposure, or clinical symptoms suggestive of cardiac dysfunction. To appropriately tailor doses of select components of chemotherapy, including thiopurines, and minimize adverse effects during treatment, pharmacogenomic testing for thiopurine methyltransferase (*TPMT*) and nucleoside diphosphate-linked moiety X-type motif (nudix hydrolase 15, *NUDT15*) should be considered. For dosing guidelines for thiopurines based on *TPMT* and *NUDT15* phenotype, see the “Pharmacogenomics” section (available online, in these guidelines, at NCCN.org).

During the workup, it is important to consider the potential influence of any ALL predisposition syndromes. A growing number of germline mutations associated with ALL risk have been reported.⁷⁵ Importantly, children with Down syndrome are at an increased risk for the development of ALL.⁷⁶ For non-Down syndrome-related ALL, most patients do not have an identifiable leukemia predisposition syndrome. An exception is low-hypodiploid ALL, in which germline *TP53* mutations are common and testing should be considered.

It should be noted that the recommendations included in the guidelines represent a minimum set of workup considerations and that other evaluations or testing may be needed based on clinical symptoms.

Procurement of cells should be considered for purposes of future research (in accordance with institutional practices or policies).

Prognostic Factors and Risk Stratification

Various disease-related and patient-specific factors may have prognostic significance in patients with ALL. In particular, patient age, WBC count, immunophenotypic/cytogenetic/genetic subtype, presence of CNS disease, and response to therapy have been identified as important factors in defining risk and assessing prognosis for both childhood and adult ALL.

Initially, risk assessment for childhood ALL was individually determined primarily by the institution, complicating the interpretation of data. However, in 1993, the Pediatric Oncology Group (POG) and Children’s Cancer Group (CCG) established a common set of risk criteria.⁷⁷ In this system, 2 risk groups were designated: standard risk and high risk. Standard risk was assigned to patients aged 1 to <10 years and with a WBC count less than 50×10^9 cells/L, whereas all other patients with ALL, including T-ALL (regardless of age or WBC count), were considered high risk.³⁰

Different cooperative groups have used a combination of clinical, biologic, and response variables to allocate patients into risk groups based on outcome.^{30,74,78}

SURVEILLANCE^{jj}

- Year 1 (every 1–2 months):
 - Physical exam, including testicular exam (where applicable),
 - CBC with differential
 - LFTs until normal
- Year 2 (every 3–6 months):
 - Physical exam including testicular exam (where applicable)
 - CBC with differential
- Year 3+ (every 6–12 months or as indicated):
 - Physical exam including testicular exam (where applicable)
 - CBC with differential

Procedures and Molecular Testing

- Bone marrow aspirate and cerebrospinal fluid (CSF) for suspected relapse
 - If bone marrow aspirate is done: Flow cytometry with additional studies that may include comprehensive cytogenetics, FISH, molecular testing, and MRD testing.
- Consider periodic *BCR-ABL1* transcript-specific quantification (Ph+ ALL)
- See Response Assessment (PEDALL-H*) for definitions of relapse

Relapse
See First Relapse Disease for
B-ALL (PEDALL-9)
or T-ALL (PEDALL-10)

Monitoring for Late Effects

- Echocardiogram as clinically indicated (related to cumulative anthracycline dose).
- Neuropsychological testing as clinically indicated given increased risk of neurotoxicity in ALL survivors.
- Monitor for healthy weight and encourage healthy lifestyle choices given increased risk of obesity in patients with history of childhood ALL.
- Refer to Survivorship recommendations in the NCCN Guidelines for Adolescent and Young Adult Oncology.[†]
- Refer to the ALL Long-term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers from the Children's Oncology Group (COG): <http://www.survivorshipguidelines.org>

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

jj Surveillance recommendations apply after completion of chemotherapy, including maintenance.

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Some cooperative groups subdivide patients into 5 or more different risk groups that are used to tailor therapy. In B-ALL, patients with high-risk or very-high-risk disease have been found to have any of the following characteristics: t(9;22) chromosomal translocation (ie, Ph-positive ALL) and/or presence of *BCR-ABL1* fusion gene; hypodiploidy (<44 chromosomes)⁷⁹; *BCR-ABL1*-like or Ph-like ALL⁵⁹; *iAMP21*^{42,80}; patients younger than age 1 with *KMT2A* gene rearrangement,^{34,80} or failure to achieve remission with induction therapy.³⁰ Conversely, criteria were refined for lower risk and included patients with hyperdiploidy, especially with simultaneous trisomies of chromosomes 4, 10, and 17,^{30,81} and the t(12;21) chromosomal translocation (*ETV6-RUNX1* subtype).⁸² The presence or absence of extramedullary disease and the early response to treatment (eg, MRD) also modified risk.

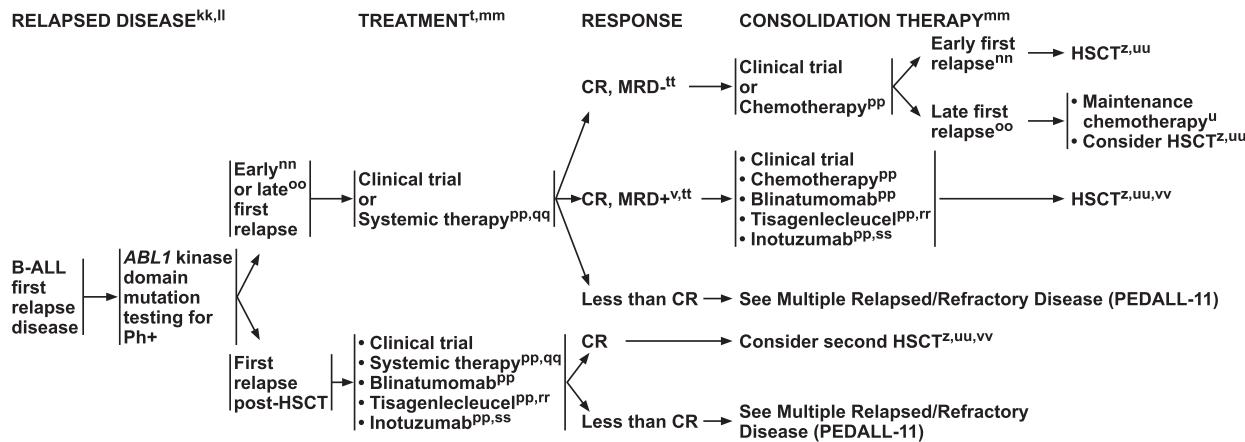
Risk stratification of T-ALL has been challenging, because other than MRD measurements, the clinical variables used to classify risk in B-ALL, including age and WBC counts, are not independently prognostic in T-ALL.⁸³ Although T-ALL is often categorized as high risk depending on the institution, newer treatment options have resulted in improved survival outcomes for these patients.^{83–86} Furthermore, the identification of genetic mutations and the use of targeted therapies may

change the way T-ALL is treated and ultimately how these patients are assessed for risk.

The POG and CCG have since merged to form the Children's Oncology Group (COG), and subsequent risk assessment has produced additional risk factors to further refine therapy.⁸⁰ In the United States, other groups have also developed standards for risk-stratified treatment approaches, including the St. Jude Consortium^{87–89} and the Dana-Farber Cancer Institute (DFCI) ALL Consortium.^{78,90,91} Initial risk stratification for these cooperative groups integrates the NCI criteria such that patients are classified as being low, standard, high, or very high risk (see “Risk Stratification Definitions, Initial Risk Group Stratification,” available online, in these guidelines, at NCCN.org). After induction remission therapy, each group applies additional risk-stratified criteria (see “Risk Stratification Definitions, Post-Induction Therapy Risk Group Stratification,” in the algorithm at NCCN.org). The Berlin-Frankfurt-Münster (BFM) Group categorizes risk based on several factors, including MRD, poor prednisone response, evidence of *MLL/AF4*, and hypodiploidy.^{92,93}

COG Approach

In the COG approach, patients with B-ALL are initially classified as standard risk (ie, aged 1 to <10 years and WBC



^uSee Principles of Systemic Therapy (PEDALL-F*).

^vThe threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information see Minimal Residual Disease (PEDALL-^{tt}*).

^zSee Principles of Hematopoietic Stem Cell Transplant (PEDALL-J*).

^{kk}Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.

^{ll}See NCCN Guidelines for Palliative Care.^t

^{mm}For Ph+ALL add TKI to the treatment; see Regimens for Relapsed/Refractory Ph-positive ALL (PEDALL-F, 8 of 12*).

ⁿⁿEarly relapse is defined as <36 mo from initial diagnosis for isolated or combined bone marrow relapse OR <18 mo from initial diagnosis for isolated EM relapse.

^{oo}Late relapse is defined as ≥36 mo from initial diagnosis for isolated or combined bone marrow relapse OR ≥18 mo from initial diagnosis for isolated EM relapse.

^{pp}See Principles of Systemic Therapy for Relapsed/Refractory ALL (PEDALL-F, 7 of 12*).

^{qq}If patients relapse >3 months from initial diagnosis, consider treatment with the same induction regimen; see Principles of Systemic Therapy (PEDALL-F*).

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count $<50 \times 10^9$ cells/L) or high risk (ie, aged ≥ 10 years and/or WBC count $>50 \times 10^9$ cells/L, CNS-3/testicular disease, t(9;22) chromosomal translocation [ie, Ph-positive ALL and/or presence of *BCR-ABL1* fusion protein, and have received steroid pretreatment]).⁸⁰ After induction, a critical measure used to ascribe risk is MRD,⁸⁰ and patients are classified as low, standard, or high risk within initial standard- or high-risk classifications. The threshold for end-of-induction (EOI) MRD has decreased from $\geq 0.1\%$ to $\geq 0.01\%$, and peripheral blood MRD is assessed at day 8 instead of day 8/day 15 bone marrow aspirates for morphology.⁸⁰ Risk stratification for T-ALL in the COG approach is primarily dependent on extramedullary disease and MRD status at both day 29 of induction and of consolidation for those patients who do not experience remission at the end of induction.⁸³ For patients requiring an end of consolidation MRD assessment, the threshold between intermediate and very high risk is $\geq 0.1\%$.⁸³

St. Jude Consortium Approach

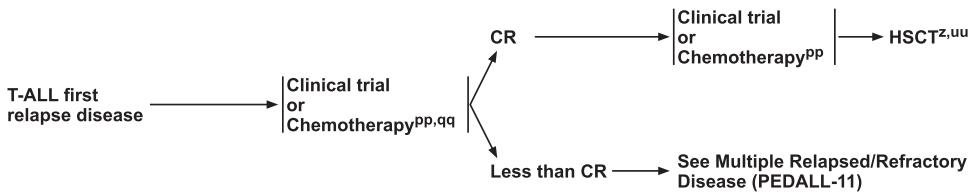
In the St. Jude Consortium approach, patients with ALL are initially classified as low risk if they present with the following features: B-ALL with DNA index ≥ 1.16 and having the *ETV6-RUNX1* fusion, or B-ALL with age 1–9.9 years and WBC count $< 50 \times 10^9$ cells/L, or if they lack standard-risk

features. Patients with standard-risk features include: B-ALL patients aged ≥ 10 years or presenting with WBC count $\geq 50 \times 10^9$ cells/L (not including DNA index ≥ 1.16 or the presence of the *ETV6-RUNX1* fusion); B-ALL patients with CNS-3 status, overt testicular leukemia, or adverse genetic features including *BCR-ABL1* fusion/t(9;22), *TCF3-PBX1* fusion/t(1;19), *KMT2A* rearrangement, hypodiploidy, *iAMP21*, or *MEF2D* fusion; or if the patients have T-ALL.⁸⁹ After induction, the same criteria hold true for low- and standard-risk groups, with an addition to the latter that estimates poor early response based on MRD ($\geq 1\%$ MRD on day 15 of remission induction, or $\geq 0.01\%$ MRD at the EOI). Patients are categorized as high risk postinduction if MRD is detectable ($\geq 1\%$ MRD at the EOI or $\geq 0.1\%$ MRD at the early intensification therapy and increasing) and/or persistent.

DFCI ALL Consortium Approach

In the DFCI ALL Consortium approach, patients with ALL are initially assigned to risk groups at day 10 of induction IA, based on the results of FISH, karyotype, and a targeted fusion NGS panel.⁹⁴ The initial grouping includes: standard risk (ie, aged 1 to <15 years, WBC count $<50 \times 10^9$ cells/L, and lacking high-risk or very-high-risk adverse biologic features); high risk (ie, disease expressing *BCR-ABL1* and

RELAPSED/REFRACTORY DISEASE^{kk,II} **TREATMENT^t** **RESPONSE** **CONSOLIDATION THERAPY**



^t See Principles of Supportive Care (PEDALL-B*).

^z See Principles of Hematopoietic Stem Cell Transplant (PEDALL-J*).

^{kk} Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.

^{II} See NCCN Guidelines for Palliative Care.[†]

^{pp} See Principles of Systemic Therapy for Relapsed/Refractory ALL (PEDALL-F, 7 of 12*).

^{qq} If patients relapse >3 months from initial diagnosis, consider treatment with the same induction regimen. See Principles of Systemic Therapy (PEDALL-F*).

^{uu} For patients with MRD-positive second CR, it is recommended to receive an additional 1–2 courses of therapy to achieve an MRD-negative result prior to allogeneic HSCT. However, some patients may not be able to achieve MRD negativity and proceeding to allogeneic HSCT should be considered.

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PEDALL-10

iAMP21, or if patients have T-ALL); or very high risk [ie, B-ALL with these features: *IKZF1* deletion, *KMT2A* rearrangement, low hypodiploidy or near haploidy, or *TCF-HLF/t(17;19)*.]⁷⁸ After induction, patients are classified as low risk if they were initially standard risk and have low MRD ($<10^{-4}$) at the EOI; or standard risk if they were initially high risk and have low MRD at the EOI. In addition, high EOI MRD and persistent MRD are features of high-risk and very-high-risk disease.

For AYA patients treated in an adult setting, see the NCCN Guidelines for ALL for additional risk stratification recommendations (available at NCCN.org).

Treatment Considerations: Phases and Agents

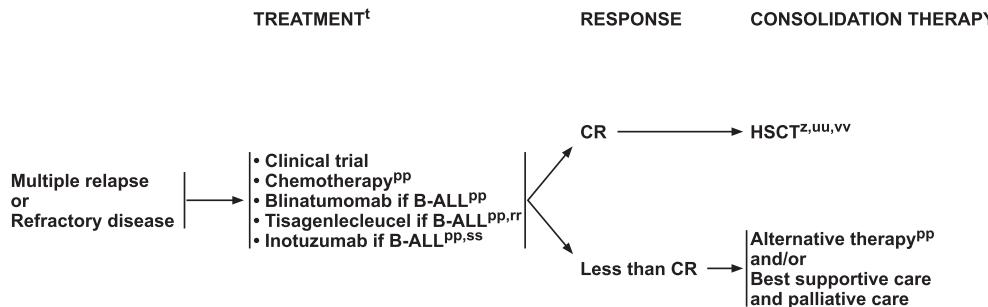
The treatment approach to ALL represents one of the most complex and intensive programs in cancer therapy. Although the specific treatment regimens and selection of drugs, dose schedules, and treatment durations differ among pediatric, AYA, and adult patients, and among different subtypes of ALL, the basic treatment principles are similar. In general, the treatment phases can be largely grouped into induction, consolidation, and maintenance. All treatment regimens for ALL include CNS prophylaxis and/or treatment. Some treatment plans may involve targeted agents and hematopoietic stem cell transplant.

Induction

Remission induction is the first block of chemotherapy with the intent of reducing tumor burden by clearing as many leukemic cells as possible from the bone marrow.⁹⁵ Induction regimens are typically based on a backbone that includes a combination of vincristine, corticosteroids (eg, prednisone, dexamethasone), and L-asparaginase/pegaspargase with or without anthracyclines (eg, daunorubicin, doxorubicin).^{87,95–97}

The BFM/COG regimens are mainly based on a 4-drug induction regimen that includes a combination of vincristine, an anthracycline, a corticosteroid, and L-asparaginase.^{93,98–101} In the COG, NCI standard risk patients are treated with a 3-drug induction that does not include anthracyclines. Some studies from the Cancer and Leukemia Group B (CALGB) have used a 5-drug regimen in AYA and adult patients, which adds cyclophosphamide to the above 4-drug combination.¹⁰²

Randomized studies comparing the use of dexamethasone versus prednisone as part of induction therapy in children with ALL showed that dexamethasone significantly decreased the risk of isolated CNS relapse and improved EFS outcomes compared with prednisone.^{103,104} The observed advantage in outcomes with dexamethasone may partly be attributed to improved penetration of

MULTIPLE RELAPSE/REFRACTORY DISEASE^{kk, ll}^t See Principles of Supportive Care (PEDALL-B*).^z See Principles of Hematopoietic Stem Cell Transplant (PEDALL-J*).^{kk} Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.^{ll} See NCCN Guidelines for Palliative Care.^t^{pp} See Principles of Systemic Therapy for Relapsed/Refractory ALL (PEDALL-F, 7 of 12*).^{rr} See Tisagenlecleucel in the Principles of Systemic Therapy (PEDALL-F, 10 of 12*).^{ss} Inotuzumab ozogamicin is not FDA approved for children and is associated with hepatotoxicity, including fatal and life-threatening hepatic veno-occlusive disease, and increased risk of post-hematopoietic stem cell transplant (HSCT) non-relapse mortality. For details, see: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/76104s000lbl.pdf.^{uu} For patients with MRD-positive second CR, it is recommended to receive an additional 1–2 courses of therapy to achieve an MRD-negative result prior to allogeneic HSCT. However, some patients may not be able to achieve MRD negativity and proceeding to allogeneic HSCT should be considered.^{vv} The role of allogeneic HSCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent HSCT. In the global registration trial, relapse-free survival was 59% at 12 months, with only 9% of patients proceeding to HSCT (Maude SL et al. N Engl J Med 2018;378:439-448). See Principles of Hematopoietic Stem Cell Transplant (PEDALL-J*).*Available online, in these guidelines, at NCCN.org. ^tTo view the most recent version of these guidelines, visit NCCN.org.Version 2.2020, 11/25/19 © National Comprehensive Cancer Network, Inc. 2020. All rights reserved.
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dexamethasone into the CNS.¹⁰⁵ Although dexamethasone is reported to significantly reduce the risks for CNS relapse and improve EFS rates compared with prednisone, significant toxicities are associated with dexamethasone including osteonecrosis and infection,^{106,107} and an advantage for OS has yet to be conclusively shown, except in the subset of T-ALL patients with prednisone good response in the AIEOP-BFM ALL 2000 study.¹⁰⁶

Several different agents exist for asparaginase depletion, including pegaspargase, *Erwinia* asparaginase, and calaspargase pegol. Compared with native *Escherichia coli*-derived L-asparaginase, pegaspargase has a longer half-life and decreased immunogenicity.^{95,108} *Erwinia* asparaginase is typically given to patients who have experienced an allergic reaction to pegaspargase, and it requires a more frequent administration schedule.⁹⁵ Calaspargase pegol is a newer asparaginase enzyme formulation with a different linker molecule that enhances its hydrolytic stability and increases its half-life relative to pegaspargase.¹⁰⁹

Consolidation

The intent of postinduction consolidation is to eliminate any leukemic cells potentially remaining after induction

therapy, further eradicating residual disease. The consolidation phase is the treatment phase most affected by risk stratification, such that lower-risk patients receive less-intensive consolidation and higher-risk patients receive consolidation that is more intensive. The postremission induction phase of treatment (but before long-term maintenance therapy) may also be described as *intensification therapy*. The combination of drugs and duration of therapy for consolidation regimens vary largely among studies and patient populations but can comprise combinations of drugs similar to those used during the induction phase. High-dose methotrexate, cytarabine, 6-mercaptopurine (6-MP), cyclophosphamide, thioguanine, vincristine, corticosteroids, and L-asparaginase/pegaspargase are frequently incorporated into consolidation/intensification regimens.^{87,95,97,100,101} This phase of treatment may involve 4 to 6 cycles of therapy and in some settings, may occur over a duration of up to 8 months.⁸⁷

Maintenance

The goal of extended maintenance or continuation therapy is to prevent disease relapse after postremission induction and consolidation therapy. Most maintenance regimens are based on a backbone of daily 6-MP and

weekly methotrexate (typically with the addition of periodic vincristine and corticosteroids) for 2 to 3 years.^{87,95,97} Factors that affect the bioavailability of 6-MP can significantly impact patient care. Oral 6-MP can have highly variable drug and metabolite concentrations among patients.^{110,111} Furthermore, age, gender, and genetic polymorphisms can affect bioavailability.^{112–114} The efficacy of maintenance therapy is determined by the metabolism of 6-MP to the antimetabolite chemotherapeutic agent 6-thioguanine nucleotide; however, other pathways compete for 6-MP, thereby reducing the amount of active metabolite produced. The 4 enzymes that metabolize 6-MP are xanthine oxidase, hypoxanthine-guanine phosphoribosyltransferase, TPMT, and NUDT15. Heterozygosity at the *TPMT* gene locus occurs in 5%–10% of the population and has been shown to have intermediate enzyme activity.^{115–117} NUDT15 deficiency is also associated with 6-MP intolerance. Therefore, determining a patient's *TPMT* and *NUDT15* genotype is recommended to optimize 6-MP dosing, especially in patients who experience myelosuppression at standard doses.¹¹⁸ For dosing guidelines for thiopurines based on *TPMT* and *NUDT15* phenotype, see "Pharmacogenomics" in the full version of the algorithm (at NCCN.org).

Noncompliance also results in undertreatment, particularly in the AYA population. Compliance issues should be addressed for patients without cytopenia. If increasing doses of 6-MP are given during maintenance but no drop in the counts is observed, this may be indicative of noncompliance.¹¹⁹ Quantification of 6-MP metabolites can be very useful in determining whether the lack of myelosuppression is due to non-compliance or hypermetabolism.

Extramedullary Disease Prophylaxis and Treatment

The goal of CNS prophylaxis and/or treatment is to prevent CNS disease or relapse by clearing leukemic cells within sites that cannot be readily accessed with systemic chemotherapy because of the blood-brain barrier. CNS-directed therapy may include intrathecal therapy (ie, intrathecal methotrexate, cytarabine, corticosteroid), cranial irradiation, and/or systemic chemotherapy (eg, dexamethasone, high-dose methotrexate, intermediate-/high-dose cytarabine, L-asparaginase).^{87,95,97,105,120} CNS prophylaxis is typically given to all patients throughout the entire course of ALL therapy, from induction, to consolidation, to the maintenance phases of treatment. Patients with testicular disease at diagnosis that is not resolved by the end of induction therapy may receive radiation to the testes.

Hematopoietic Stem Cell Transplantation

Allogeneic HSCT has demonstrated improved clinical outcomes in pediatric patients with ALL with evidence of

certain high-risk features and/or persistent disease.^{87,121,122} In addition, survival rates appear to be comparable regardless of the stem cell source (matched related, matched unrelated, cord blood, or haploidentical donor).^{122,123} The benefit of allogeneic HSCT in infants with ALL is controversial, although some studies have shown a role in high-risk patients with *KMT2A* rearrangements and other poor risk factors.^{87,124,125} Based on the data, it is reasonable to consider HSCT in first remission (CR1) for certain patients as described in the HSCT sections throughout the discussion.

Targeted Agents

The emergence of targeted therapies for hematologic malignancies, including the treatment of Ph-positive disorders with TKIs, represents an important advancement in ALL therapy.^{126–130} Clinicians should be aware of variation among the TKIs relating to absorption from the gastrointestinal tract. Additionally, histamine-2 antagonist or proton pump inhibitors (PPIs) can affect the bioavailability of some TKIs. In Ph-like ALL cases harboring *CRLF2* and *JAK* alterations, the utility of Janus kinases inhibitors are being explored.¹³¹ The purine nucleoside analog nelarabine has been approved for the treatment of R/R T-ALL or lymphoblastic lymphoma.¹³² Monoclonal antibodies to surface antigens such as CD19, CD20, CD22, and CD52 have been used in unconjugated form (eg, rituximab, epratuzumab), conjugated to immunotoxins or chemotherapeutic agents (moxetumomab, inotuzumab ozogamicin [InO]), or in the form of a bispecific antibody (blinatumomab).^{87,133–135} Chimeric antigen receptor (CAR) T cells that target CD19 have demonstrated durable remissions in pediatric and AYA patients with R/R B-ALL.¹³⁶ Overall, these agents may be incorporated as part of frontline induction, consolidation, and/or maintenance regimens during the course of initial ALL therapy, and in R/R disease settings.

Management of Ph-Negative or Ph-Like B-ALL

Front-line Management of Patients With Ph-Negative or Ph-Like ALL

The management of de novo Ph-negative and Ph-like B-ALL is complex, and current regimens are based on a number of recently completed or ongoing trials referenced in the algorithm, which are summarized in the next sections.

COG AALL0331 and AALL0932

The COG AALL0331 trial helped establish the benefit of intensifying therapy for patients with EOI MRD >0.01%, which is now part of all COG protocols. This trial enrolled 5,311 patients with standard-risk B-ALL and used a 3-drug induction without anthracyclines (ie, dexamethasone,

vincristine, and pegaspargase), with postinduction assignment into refined risk groups based on genetics and early response (ie, standard-risk low, standard-risk average, and standard-risk high).¹³⁷ At the EOI, patients were randomized to receive standard consolidation (6-MP, vincristine, and intrathecal methotrexate) versus intensified consolidation (cyclophosphamide, cytarabine, 6-MP, vincristine, pegaspargase, and intrathecal methotrexate).¹³⁷ For standard-risk low patients (ie, leukemic blasts were positive for triple trisomies of chromosomes 4, 10, and 17 or were positive for *ETV6-RUNX1* plus day 8 [or day 15] M1 bone marrow and day 29 MRD <0.1%), the 5-year EFS and OS rates were 95% and 99%, respectively. The 5-year EFS and OS for all evaluable patients with standard risk disease was 89% and 96%, respectively, and intensified consolidation did not significantly improve outcomes for standard-risk average patients.¹³⁷ Standard-risk high patients (day 15 bone marrow ≥5% blasts and/or day 29 MRD ≥0.1%) were nonrandomized to intensified consolidation and 2 intensified IM and DI phases, resulting in 5-year EFS and OS rates of 85% and 94%, respectively.¹³⁷

Due to the intensification of premaintenance therapy and modern risk stratification,¹³⁸ the COG AALL0932 study, a randomized phase III trial, was designed to optimize maintenance therapy in newly diagnosed pediatric B-ALL by asking 2 questions: (1) will a higher dose (40 mg/m²/dose) for weekly oral methotrexate be superior to standard dose (20 mg/m²/dose); and (2) will a reduced frequency of vincristine and dexamethasone pulses (from every 4 weeks to every 12 weeks) impact outcomes? The 5-year DFS estimates for average risk patients who received oral methotrexate 20 mg/m²/dose versus 40 mg/m²/dose were similar (95% ± 2.4% vs 92.3% ± 2.9%; *P*=.95), suggesting that escalation of the methotrexate starting dose does not improve outcomes.¹³⁹ The 5-year DFS (±standard error) for the average risk patients randomized to receive vincristine and dexamethasone pulses every 4 weeks versus every 12 weeks was 94.1% ± 1.0% vs 95.1% ± 0.9% (one-sided *P*=.86).¹³⁸

COG AALL0232 and AALL1131

The AALL0232 trial enrolled 2,154 patients between the ages of 1 and 30 years who were diagnosed with high-risk B-cell ALL.¹⁴⁰ In this study, patients were randomly assigned to receive dexamethasone versus prednisone during induction and HD-MTX versus C-MTX plus pegaspargase during IM1. HD-MTX showed improved 5-year EFS (80% vs 75%; *P*=.008) and OS (88.9% ± 1.2% vs 86.1% ± 1.4%; *P*=.25) rates compared with C-MTX. No statistically significant difference was reported in the occurrence of mucositis, neurotoxicity, osteonecrosis, or other toxicities. The ALL0232 trial compared dexamethasone 10 mg/m²/day for 14 days to prednisone 60 mg/m²/day for 28 days. Dexamethasone showed improved outcomes

during induction in patients younger than 10 years of age; however, it was associated with a higher risk of osteonecrosis in patients 10 years of age or older. These data suggest that age may be an important factor for the selection of a corticosteroid.¹⁴⁰

Relative to pediatric patients with standard risk B-ALL, patients with high-risk B-ALL experience high relapse rates and worse clinical outcomes.^{128,141} Some approaches to combat this are investigating the integration of new agents into treatment after induction. The COG AALL1131 study was a phase III trial for patients aged 1–30 years with newly diagnosed high-risk B-ALL.^{142,143} Patients enrolled on this trial received a standard 4-drug induction (dexamethasone/prednisone, vincristine, daunorubicin, and pegaspargase). One experimental arm of this study was designed to evaluate the safety and efficacy of clofarabine, cyclophosphamide, and etoposide as part of multiagent chemotherapy.¹⁴³ However, infectious toxicities precipitated the closure of this study arm. Another experimental arm investigated whether substituting post-induction chemotherapy (cyclophosphamide, cytarabine, and mercaptopurine) with cyclophosphamide and etoposide would improve the 4-year DFS of pediatric patients with very high risk B-ALL.¹⁴² This substitution was not superior to the control arm. Given this experience, future therapeutic approaches will examine the utility of targeted agents. In this context, the COG has investigated the incorporation of dasatinib for newly diagnosed high-risk patients with Ph-like B-ALL harboring *ABL*-class lesions (AALL1131),⁵⁹ and is investigating ruxolitinib for high-risk patients with newly diagnosed Ph-like ALL harboring *CRLF2* rearrangements and/or a mutation that activates JAK-STAT pathway (AALL1521).¹⁴⁴ In addition, ongoing trials are investigating whether the combination of immunotherapies with chemotherapy improves outcomes in certain subsets of patients (blinatumomab in standard-risk B-ALL: COG AALL1731; inotuzumab ozogamicin in high-risk B-ALL: COG AALL1732).

DFCI ALL Protocols 05-001 and 16-001

The DFCI ALL Consortium Protocol 05-001 enrolled 678 children and adolescent patients (aged 1–18 years of age) with newly diagnosed Ph-negative B-ALL, and tested a new risk stratification system.⁷⁸ At study entry, patients were classified as standard risk or high risk and a 4-drug induction was used (prednisone, vincristine, doxorubicin, and pegaspargase).⁷⁸ After achieving complete remission, patients with high EOI MRD (≥10⁻³ via PCR analysis of patient-specific immunoglobulin or T-cell receptor rearrangements) and/or adverse cytogenetics (*KMT2A* rearrangement or hypodiploidy) were reclassified as very high risk and received intensified therapy.⁷⁸ Among all patients, the 5-year EFS and OS rates were 87% (95% CI, 84%–89%) and 93% (95% CI, 90%–94%), respectively.

The 5-year DFS rates for standard-risk ($n=407$), high-risk ($n=176$), and very-high-risk ($n=65$) patients were 94%, 84%, and 79%, respectively.

To refine risk classification for future trials, the prognostic significance of alternative age and WBC count thresholds, alternative EOI MRD levels, and *IKZF1* deletion status were examined. The *IKZF1* deletion was associated with inferior 5-year EFS and higher cumulative incidence of relapse, including among patients with low MRD.⁷⁸ Further analysis of outcome by age demonstrated that patients aged 10 to 14.99 years with Ph-negative B-ALL had similar EFS to those <10 years of age, whereas those ≥ 15 years of age had a significantly worse outcome.⁷⁸ In an ongoing trial, DFCI protocol 16-001 incorporates some changes to risk stratification for B-ALL, including the use of (1) 15 years as a cut-off to distinguish standard and high-risk patients; (2) prospective determination of *IKZF1* deletion status; and (3) assessment of MRD via NGS assay to identify patients at very high risk.⁷⁸

St. Jude Total Therapy XV and XVII Studies

In the St. Jude Total XV Study, 498 evaluable patients with newly diagnosed ALL (aged 1–18 years of age) were enrolled, with study aims of determining whether prophylactic cranial irradiation could be safely omitted in all patients and determining the impact on overall EFS.⁸⁸ Induction was comprised of multiagent chemotherapy (prednisone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide, cytarabine, and 6-MP), and on hematopoietic recovery, MRD was assessed before intensified consolidation/continuation therapy according to risk-stratified groups. Of 498 patients, 492 (98.8%) entered complete remission (low risk, 99.6%; standard risk, 99.5%; and high risk, 90.4%). The 5-year EFS and OS estimates were 85.6% and 93.5%, respectively.⁸⁸ This study demonstrated that prophylactic cranial irradiation could be omitted without compromising OS.

The ongoing Total XVII Study will incorporate novel precision medicine strategies based on genomic features and targeted treatment.⁷⁴ Some of these approaches include the use of NGS-based diagnostics. In addition, the Total XVII study will investigate the use of dasatinib in patients with *ABL*-class chimeric fusions identified by RNA sequencing, and ruxolitinib in patients with alterations that activate the JAK-STAT signaling pathway.⁷⁴

Blinatumomab

Blinatumomab is a bispecific T-cell engaging antibody that directs CD3-positive effector memory T cells to CD19-positive target cells, inducing cell death.^{145,146} Blinatumomab first showed promising clinical efficacy as a means of eradicating persistent MRD after upfront chemotherapy. In a multicenter, single-arm, phase II

study, Topp et al¹³⁵ evaluated the efficacy of blinatumomab in MRD-positive patients with Ph-negative B-ALL ($n=21$; age range, 20–77 years). Patients were considered MRD-positive if they had never experienced MRD negativity before blinatumomab, or had experienced a hematologic remission with MRD $\geq 10^{-4}$. After blinatumomab treatment, 16 of 20 evaluable patients were determined to be MRD-negative at a detection threshold of 10^{-4} .¹³⁵ After a median follow-up of 33 months, the hematologic recurrence-free survival of the evaluable cohort was 61%.¹⁴⁷ Gökbüget et al¹⁴⁸ examined the efficacy of blinatumomab in an expanded cohort ($n=116$; age range, 18–76 years) using a higher threshold for MRD positivity (hematologic CR with MRD $\geq 10^{-3}$). After one 28-day cycle of blinatumomab, 88 of 113 evaluable patients experienced a complete MRD response, and the recurrence-free survival rate at 18 months was 54%.¹⁴⁸ In both of these trials, most patients achieving MRD negativity after blinatumomab proceeded to allogeneic HSCT, establishing blinatumomab as an effective “bridge to transplant” in MRD-positive patients. Subsequent studies of blinatumomab evaluated its ability to induce complete remission (including rapid MRD-negative responses) in pediatric and adult patients with R/R B-precursor ALL.^{134,149–151} In March 2018, the FDA approved blinatumomab use for the treatment of adult and pediatric patients with B-cell precursor ALL in first or second CR with MRD defined as disease $\geq 0.1\%$ (see “Management of Patients with Relapsed or Refractory Ph-Negative or Ph-Like ALL,” below, for discussion of studies related to blinatumomab use in R/R B-ALL).

Hematopoietic Stem Cell Transplant

For pediatric and AYA patients with Ph-negative ALL in CR1, allogeneic HSCT may be considered for patients who (1) remain MRD positive at the end of consolidation (regardless of genetic features); or (2) have high-risk genetic features and are MRD-positive at EOI.¹⁴¹ In the latter group, it should be noted that some studies have examined the role of HSCT in pediatric patients with hypodiploid B-ALL, and it is unclear whether HSCT improves outcomes when given in CR1 in patients who are MRD-positive at the EOI.^{152–155} However, HSCT for hypodiploid ALL may be considered in the context of a clinical trial.

Management of Patients With Relapsed or Refractory Ph-Negative or Ph-Like ALL

The outcomes of pediatric patients with R/R B-ALL has been historically poor. In addition, the number of previous salvage attempts and duration of CR1 impacts outcomes.^{156–158} In the guidelines, early relapse is defined as disease that recurs less than 36 months from initial diagnosis for isolated or combined BM relapse or less

than 18 months from initial diagnosis for isolated extramedullary relapse. Late relapse is defined as disease that recurs greater than or equal to 36 months from initial diagnosis for isolated or combined BM relapse or greater than or equal to 18 months from initial diagnosis for isolated extramedullary relapse. In general, HSCT is the only known curative therapy for early relapse of B-ALL. For patients with late relapses of B-ALL or late isolated CNS relapses of T-ALL, chemotherapy alone may be sufficient.^{157,159} It has also been reported that patients who received chimeric antigen receptor (CAR) T cells can maintain long-term remission without subsequent HSCT.¹³⁶ Several trials referenced in the algorithm have developed regimens that are currently used to treat R/R B-ALL, and these studies are summarized in the subsequent sections.

ALL-REZ BFM 90

The ALL Relapse BFM 90 (ALL-REZ BFM 90) trial was designed to improve prognosis for pediatric patients with relapsed ALL (<19 years of age; n=525) through additional multichemotherapy blocks.¹⁶⁰ The patients were stratified into 3 risk groups: A (early bone marrow relapses; n=126); B (late bone marrow relapses; n=183); and C (isolated extramedullary relapses; n=64). Patients with early bone marrow or T-ALL relapse (poor prognosis group) were eligible for experimental regimens. In addition, 117 patients received HSCT. After treatment with this regimen, 440 patients (84%) experienced second CR (CR2), 25 patients died during induction, and 60 patients (11%) did not show response. Most patients in each group experienced CR2 (group A: 83%; group B: 94%, and group C: 100%).¹⁶⁰ Significant differences existed between strategic groups: probability of EFS/pEFS(A)=0.17±0.03; pEFS(B)=0.43±0.04; pEFS(C)=0.54±0.06; pEFS(poor prognosis group) =0.15±0.03; log-rank P<.0001.¹⁶⁰ Significant predictors of EFS in multivariate analyses included time point, site of relapse, immunophenotype, and HSCT.¹⁶⁰

COG AALL01P2

In the COG AALL01P2 study, 124 pediatric patients aged 1 to 21 years with relapsed ALL were treated with 3 blocks of reinduction chemotherapy, with an upfront randomization in block order (arm A = blocks 1, 2, 3; arm B = blocks 1, 3, 2).¹⁶¹ Patients with CNS leukemia were non-randomly assigned to arm B to allow early introduction of high-dose cytarabine, and patients with mature B-ALL and Down syndrome were excluded.¹⁶¹ In addition, patients with Ph-positive ALL received imatinib with all chemotherapy blocks. Of 117 patients evaluable for response in block 1, 81.2% experienced a CR2. For early relapses (defined as recurrence <36 months after initial diagnosis) versus late relapses (defined as recurrence ≥36 months after initial diagnosis), the CR2 rates were 68% ± 6% and 96% ± 3% (P<.0001), respectively.¹⁶¹

One objective of this study was to determine the feasibility of measuring MRD in a single COG central reference laboratory at the completion of each block to monitor the kinetics of response. The absence of MRD at the end of the first month of reinduction therapy was associated with better outcomes in all patients.¹⁶¹ In addition, subsequent blocks of therapy reduced the MRD burden in 40 (71%) of 56 patients who were MRD positive after block 1.

UKALL R3

The UKALL R3 trial investigated the outcomes of pediatric patients with relapsed ALL aged 1 to 18 years (n=239).¹⁵⁹ Patients were stratified into standard-, intermediate-, or high-risk groups based on the duration of CR1, site of relapse, and immunophenotype. In addition, patients were randomized to receive mitoxantrone or idarubicin on days 1 and 2 of induction.¹⁵⁹ After 3 blocks of therapy, all patients in the high-risk group and patients in the intermediate-risk group with post-induction high MRD ($\geq 10^{-4}$ cells) received HSCT. The estimated 3-year PFS and OS rates in the mitoxantrone versus idarubicin groups were 64.6% versus 35.9% (P=.0004); and 69% versus 45.2% (P=.004), respectively.¹⁵⁹ After a median follow-up of 84 months, PFS of all randomly assigned patients was 60% (95% CI, 54%–70%). Of 92 patients who received HSCT, 58 (63%) remained in CR2, 13 (14%) died of complications, and 21 (23%) experienced relapse after HSCT.¹⁵⁷ Of 70 patients who continued on chemotherapy, 49 (70%) remained in CR2, 2 (3%) died of complications, and 19 (27%) experienced relapse. At 5 years, the PFS was 56% (95% CI, 46%–65%) in patients with high MRD and 72% (95% CI, 60%–81%) in patients with low MRD ($< 10^{-4}$ cells; P=.0078).¹⁵⁷

COG AALL07P1

Bortezomib is a proteasome inhibitor that has demonstrated some activity in relapsed pediatric ALL.^{162–165} The COG AALL07P1 phase II study tested the hypothesis that adding bortezomib to reinduction chemotherapy in pediatric patients experiencing first relapse would increase CR2 rates.^{162,163} Of the evaluable patients treated with bortezomib and chemotherapy (n=135; B-ALL, n=103; T-ALL, n=22; T-lymphoblastic lymphoma, n=10), overall CR2 rates were 68% ± 5% for patients with precursor B-ALL (<21 years of age), 63% ± 7% for patients with very early relapse (<18 months from diagnosis), and 72% ± 6% for those with early relapse (18–36 months from diagnosis).¹⁶³ The CR2 rate for patients with relapsed T-ALL was 68% ± 10%.

Clofarabine-Based Regimens

Clofarabine is a second-generation purine analog that has shown single-agent activity in R/R pediatric ALL^{166,167}

and is approved by the FDA as monotherapy for pediatric patients aged 1 to 21 years with R/R ALL treated with at least 2 previous regimens. Other clinical studies have evaluated its use in combination with chemotherapy.^{168,169} A phase II study evaluated the efficacy and safety of clofarabine, etoposide, and cyclophosphamide in pediatric patients with R/R ALL (aged 1–21 years; n=25).¹⁶⁸ The overall response rate was 44% (7 CR, 4 complete remission with partial recovery) with a 67.3-week median duration or remission censored at last follow-up.¹⁶⁸

Fludarabine-Based Regimens

A regimen of high-dose cytarabine and fludarabine followed by granulocyte colony-stimulating factor (ie, FLAG alone) or combined with idarubicin (FLAG-IDA) yields response rates ranging from 39% to 83% in adult patients with R/R ALL.^{170–173} In a study by Gabriel et al,¹⁷⁴ 32 pediatric patients (median age, 10.4 years; range, 1.7–15.5 years) with high risk leukemias, including relapsed ALL (n=13), primary refractory ALL (n=3), relapsed acute myeloid leukemia (AML; n=13), primary refractory AML (n=1), and secondary AML (n=2), were given the FLAG-IDA regimen. Overall, 23 (71.9%) of 32 patients experienced a CR after a single course of FLAG-IDA. In patients with relapsed ALL, 10 (76.9%) of 13 achieved a CR, and in patients with primary refractory ALL, 2 of 3 achieved a CR—1 after a second course of FLAG-IDA—and both had Ph-positive disease.¹⁷⁴ Overall, 22 of the 23 patients who experienced remission (10 AML and 12 ALL) proceeded to HSCT after further consolidation with 2 to 3 courses of the FLAG regimen.

High-Dose Cytarabine-Based Regimens

In a study by the CCG, 52 pediatric patients with R/R ALL received high-dose cytarabine and L-asparaginase.¹⁷⁵ By day 28, 10 patients had died of the disease and treatment-related complications. Of the 42 evaluable patients, 22 (42% of all patients) experienced CR2.¹⁷⁵ However, 16 of the 22 patients who entered CR2 subsequently experienced relapse, and the median duration of CR2 was 3 months (range, 0.7–19 months).¹⁷⁵

Blinatumomab

A component of the growing arsenal of immunotherapies for cancer treatment, blinatumomab is a bispecific anti-CD3/CD19 monoclonal antibody that showed high CR rates (69%; including rapid MRD-negative responses) in AYA and adult patients with R/R B-precursor ALL (n=25).^{151,176} Blinatumomab was approved by the FDA based on data from a large phase II confirmatory study of 189 AYA and adult patients with R/R Ph-negative B-cell ALL that showed a CR or CR without platelet recovery in 43% of patients within the first 2 cycles of treatment.^{150,177} In a follow-up prospective, multicenter, randomized,

phase III trial, patients with R/R B-cell precursor ALL (n=405) were assigned to receive either blinatumomab (n=271) or standard chemotherapy (n=134).¹⁴⁹ The OS was longer in the blinatumomab group, with median OS at 7.7 months, compared with the standard chemotherapy group, with median OS at 4.0 months (95% CI, 0.55–0.93, P=.01).¹⁴⁹ Remission rates within 12 weeks after treatment initiation were significantly higher in the blinatumomab group than in the standard chemotherapy group with respect to both CR with full hematologic recovery (CR, 34% vs 16%; P<.001) and CR with full, partial, or incomplete hematologic recovery (CR, CRh, or CRI, 44% vs 25%; P<.001).¹⁴⁹ Of note, pre-specified subgroup analyses of patients with high bone marrow count (≥50%) at relapse demonstrated lower blinatumomab-mediated median survival and remission rates.¹⁴⁹

In a phase I/phase II open-label study, the safety and efficacy of blinatumomab was evaluated in children younger than 18 years of age with R/R B-ALL.¹³⁴ Based on phase I data, the recommended dosage of blinatumomab was 5 µg/m²/day for the first 7 days, followed by 15 µg/m²/day afterward.¹³⁴ Of the 70 patients who received this dosage, 27 (39%) experienced CR within the first 2 cycles, 14 (52%) of whom achieved complete MRD response.¹³⁴

There are significant and unique side effects to blinatumomab treatment compared with the current standard-of-care regimens. In addition, blinatumomab requires prolonged exposure for efficacy due to a short half-life (mean ± standard deviation [SD]) of 1.25±0.63 hours.^{178,179} The most significant toxicities noted in clinical studies are CNS events and cytokine release syndrome (CRS). Neurologic toxicities have been reported in 50% of patients (median onset, 7 days) and grade 3 or higher neurologic toxicities, including encephalopathy, convulsions, and disorientation, have occurred in 15% of patients.¹⁷⁸ CRS typically occurs within the first 2 days after start of blinatumomab infusion.¹⁷⁸ Symptoms of CRS include pyrexia, headache, nausea, asthenia, hypotension, increased transaminases, and increased total bilirubin. The incidence of adverse events can be reduced with monitoring for early intervention at onset of symptoms. However, the serious nature of these events underscores the importance of receiving treatment in a specialized cancer center that has experience with blinatumomab.

CAR T Cells

One of the early treatments for patients with advanced ALL included adoptive cell therapy to induce a graft-versus-leukemia effect through allogeneic HSCT or donor lymphocyte infusions. However, this method resulted in a significant risk of graft-versus-host disease. To circumvent

this issue, current advances are focused on the use of the patient's own T cells to target the B-ALL cells. The generation of CAR T cells to treat B-ALL is a significant advancement in the field.^{136,180–182} The treatment of patients with CAR T cells has served as a bridge for transplant, enabling patients who were formerly unable to receive a transplant due to poor remission status to achieve a CR and ultimately transplantation. It is also reported that patients who received CAR T cells can maintain long-term remission without subsequent HSCT.¹³⁶ CAR T cell therapy relies on the genetic manipulation of a patients' T cells to generate a response against a leukemic cell-surface antigen, most commonly CD19.¹⁸³ Briefly, T cells from the patient are harvested and engineered with a receptor that targets a cell surface tumor-specific antigen (eg, CD19 antigen on the surface of leukemic cells). The ability of CAR T cells to be reprogrammed to target any cell-surface antigen on leukemic cells is advantageous and avoids the issue of tumor evasion of the immune system via receptor downregulation, and studies of CAR T cells targeting antigens other than CD19 are ongoing.¹⁸³ The manufacture of CAR T cells currently requires ex vivo viral transduction, activation, and expansion over several days to weeks to produce a sufficient cell number to engender disease response.¹⁸⁴ Following infusion, debulking of tumors occurs in less than a week and these CAR T cells may remain in the body for extended periods of time to provide immunosurveillance against relapse.

There are several clinical trials using CAR T cells that differ in the receptor construct for patients with R/R ALL. A modified receptor, termed 19-28z—which links the CD19 binding receptor to the costimulatory protein CD28—demonstrated an overall CR in 14 of 16 patients with R/R B-cell ALL following infusion with CAR T cells.¹⁸⁵ In addition, 7 of 16 patients were able to receive an allogeneic HSCT, suggesting that CAR T cells may provide a bridge to transplant.¹⁸⁵ No relapse was observed in patients who had allogeneic HSCT (follow-up, 2–24 months); however, 2 deaths occurred from transplant complications. Follow-up data of adult patients enrolled on this trial (n=53) showed an 83% CR rate after the infusion and 32 patients achieved an MRD-negative CR.¹⁸⁶ At a median follow-up of 29 months (range, 1–65), the median OS was 12.9 months (95% CI, 8.7–23.4 months).¹⁸⁶ KTE-C19 uses a similar anti-CD19 CAR construct and demonstrated an MRD-negative CR in 6 of 8 efficacy-evaluable adult patients with R/R ALL.¹⁸⁷

A second receptor construct defined by the attachment of an alternative costimulatory protein, 4-1BB, to the CD19 binding protein has shown similar results to the 19-28z CAR T cells in terms of overall CR.¹⁸⁸ These cells, more simply referred to as CTL019, were infused into 16 children and 4 adults with R/R ALL; a CR after therapy was achieved in 14 patients.¹⁸⁸ There was no

response of the disease to treatment in 3 patients and disease response to therapy was still under evaluation for 3 patients.¹⁸⁸ A follow-up study of 25 children and 5 adults showed a morphologic CR in 90% (27 of 30) of patients within a month of treatment and an OS of 78% (95% CI, 65%–95%) and EFS of 78% (95% CI, 51%–88%) at 6 months.¹⁸⁹ There were 19 patients in sustained remission, 15 of whom received no further therapy. The ELIANA trial of CTL019/tisagenlecleucel in 75 children and young adults with R/R B-ALL demonstrated an overall remission rate of 81% within 3 months of infusion, all of which were notably MRD negative.¹³⁶ This high response rate was associated with OS rates of 90% and 76% at 6 and 12 months, respectively. As with blinatumomab, T-cell activation was accompanied by severe CRS and neurologic toxicity, as well as higher infectious risks—though treatment-related mortality remains low.¹³⁶ Given these data, CTL019/tisagenlecleucel was recommended for accelerated approval by the FDA oncologic drug advisory committee in July 2017 and fully approved by the FDA in August 2017 for the treatment of patients up to age 25 years (aged <26 years) with R/R precursor B-cell ALL.

The side effect profile of CAR T cells differs substantially from those observed with standard therapies (ie, chemotherapy, HSCT). Although side effects from CAR T cells may be severe, they have been reversible. Adverse events are attributed to CRS and macrophage activation that occur in direct response to adoptive cell transplant, resulting in high fever, hypotension, breathing difficulties, delirium, aphasia, and neurologic complications. Tocilizumab, a monoclonal antibody against interleukin-6 receptor and antagonist of interleukin-6, and corticosteroids are the main options used to manage CRS and neurotoxicity symptoms.^{190,191} Several groups have developed comprehensive guidelines regarding grading systems for and management of CAR T-cell-associated toxicities.^{192,193}

Inotuzumab Ozogamicin

Inotuzumab ozogamicin (InO) is a calicheamicin-based antibody-drug conjugate targeting CD22. Following the generation of encouraging single-agent phase II data,¹⁹⁴ a randomized study was conducted comparing InO with standard intensive chemotherapy regimens in Ph-negative or Ph-positive ALL in first or second relapse, defined as >5% marrow blasts (n=326). Compared with standard therapy, InO produced a significantly higher CR/CRi rate (80.7% vs 29.4%; P<.001), and higher MRD-negative rates (78.4% vs 28.1%; P<.001).¹⁹⁵ Notably, responses were consistent across most subgroups, including those with high marrow burden, and those with Ph-positive leukemia. The overall incidence of severe adverse events was similar across treatment arms, with a higher incidence of hepatic veno-occlusive disease

observed in the inotuzumab group, related in part to dual alkylator-based transplant conditioning administered in remission. These data translated into a significant benefit in the median duration of remission (4.6 vs 3.1 months; $P=.03$), median PFS (5 vs 1.8 months; $P<.001$), and mean OS (13.9 vs 9.9 months; $P=.005$).¹⁹⁵ In August 2017, InO received full approval from the FDA for the treatment of adults with R/R precursor B-cell ALL.

However, pediatric experience with InO is limited. In a retrospective study of pediatric patients with R/R B-ALL ($n=51$) who received InO in a compassionate use program, 67% of patients achieved CR and a majority of the responders were MRD-negative (71%).¹⁹⁶ None of the patients developed sinusoidal obstruction syndrome (SOS) during therapy, but 52% of patients who underwent HSCT following InO (11 of 21; 52%) developed SOS.¹⁹⁶

Hematopoietic Stem Cell Transplant

For patients with early relapse of B-ALL, HSCT is the only currently established curative modality. The CIBMTR group conducted an analysis of outcomes of patients with ALL ($n=582$; median age, 29 years; range, <1–60 years) who underwent transplant during relapse.¹⁹⁷ At 3 years, OS rates were 16% (95% CI, 13%–20%).¹⁹⁷ Based on findings from evidence-based review of the published literature, the American Society for Transplantation and Cellular Therapy guidelines recommend HSCT for pediatric patients with ALL in CR2 after experiencing an early marrow relapse.¹⁹⁸

NCCN Recommendations for Ph-Negative or Ph-Like ALL

Front-line Management

The panel recommends that pediatric and AYA patients with Ph-negative or Ph-like ALL be treated in a clinical trial when possible. In the absence of an appropriate clinical trial, patients are initially grouped according to risk criteria (see PEDALL-3, page 85), and induction therapy consists of multiagent chemotherapy. Patients who are MRD negative after induction will continue risk-stratified therapy. Patients who are MRD positive after induction may undergo intensified consolidation therapy. If MRD remains persistent, other options include blinatumomab or tisagenlecleucel (category 2B recommendation). In all cases, HSCT may be considered as part of consolidation or maintenance therapy (see PEDALL-4, page 86).

R/R Management

For pediatric and AYA patients with Ph-negative or Ph-like ALL experiencing early or late first relapse, the panel recommends initial treatment with systemic therapy (see PEDALL-9, page 91). If patients experience CR (CR2) and are MRD negative, the options are to

continue on chemotherapy and receive maintenance therapy or HSCT if feasible based on the risk of subsequent relapse. If patients experience CR2 and are MRD positive, or are experiencing first relapse after a prior HSCT, in addition to chemotherapy, blinatumomab, tisagenlecleucel, and inotuzumab ozogamicin may be considered prior to either a first or second HSCT. If patients experience less than a CR (ie, multiple relapse), treatment options include chemotherapy, blinatumomab, tisagenlecleucel, or InO, and they may receive HSCT as consolidation therapy if their disease subsequently responds to therapy (see PEDALL-11, page 93). Long-term remissions have been also reported after tisagenlecleucel treatment without subsequent HSCT.¹³⁶ If the disease does not respond to therapy, alternative treatment options may be considered with best supportive and palliative care (PEDALL-11, page 93).

Management of Ph-Positive B-ALL

Ph-positive ALL is relatively rare in pediatric patients, and the development of TKIs has improved previously poor treatment outcomes.⁵⁴ The management of Ph-positive B-ALL as outlined in this discussion based on a number of clinical trials referenced in the algorithm, which are summarized below.

Front-line Management of Patients With Ph-Positive ALL

COG AALL0031 and AALL0622

In a multicenter study (COG AALL0031), children and adolescents with Ph-positive ALL ($n=92$; aged 1–21 years) were treated with an intensive chemotherapy regimen combined with imatinib (340 mg/m²/day; given during postremission induction therapy and maintenance).¹²⁸ Among the cohort ($n=44$) who received continuous imatinib exposure (280 consecutive days before maintenance initiation), the 3-year EFS rate was 80.5% (95% CI, 64.5%–89.8%). This outcome compared favorably with that of a historical population of patients with Ph-positive ALL ($n=120$) treated on a POG protocol, which showed a 3-year EFS rate of only 35% ($P<.0001$).¹²⁸ Moreover, the 3-year EFS rates were similar among the groups of patients who received chemotherapy combined with continuous imatinib (88%; $n=25$) or allogeneic HSCT from a related donor (57%; $n=21$) or unrelated donor [URD] (72%; $n=11$). No major toxicities were found to be associated with the addition of imatinib to the intensive chemotherapy regimen.¹²⁸ Subsequent follow-up after 5 years confirmed these outcomes.¹²⁹ In a phase II single-arm trial (COG AALL0622) of children and young adults with Ph-positive ALL ($n=60$; aged 1–30 years), imatinib was replaced with dasatinib on induction day 15 and combined with the same chemotherapy

used in COG AALL0031.¹³⁰ The 5-year OS and EFS rates (\pm SD) were $86\% \pm 5\%$ and $60\% \pm 7\%$, respectively, and outcomes were similar to those observed in COG AALL0031.¹³⁰

EsPhALL

The European intergroup study of postinduction treatment of Ph-chromosome positive ALL (EsPhALL) reported results of the randomized open-label trial designed to evaluate the safety and long-term efficacy of discontinuous postinduction imatinib plus chemotherapy with the BFM backbone intensive treatment versus chemotherapy alone.¹²⁷ The study enrolled 108 good-risk and 70 poor-risk patients aged 1 year to 18 years. Good-risk patients were randomized 1:1 and poor-risk patients were all assigned to receive chemotherapy plus imatinib. There was a trend toward improved 4-year DFS for good-risk patients who received imatinib plus chemotherapy versus those who received chemotherapy alone (72.9% vs 61.7%; $P=.24$). In the as-treated analysis, good-risk patients who received imatinib with chemotherapy had a 4-year EFS of 75.2% versus 55.9% in patients who did not receive imatinib ($P=.06$). The incidence of serious adverse events was not statically different between the 2 groups ($P=.64$).¹²⁷ Enrollment in this trial was stopped in 2009 following results of the COG AALL0031 study that demonstrated a benefit of continuous imatinib. The EsPhALL study was amended into a single-arm study to add continuous imatinib on induction day 15, with 97% of patients achieving first CR.¹²⁶ However, the 5-year EFS and OS rates (57% and 71.8%, respectively) were similar in cohorts that received discontinuous postinduction imatinib and continuous imatinib plus chemotherapy with the BFM backbone intensive treatment.^{126,127} Additionally, a phase II trial evaluated the safety and efficacy of adding continuous dasatinib at day 15 to the intensive BFM regimen in pediatric patients with newly diagnosed Ph-positive ALL ($n=109$ enrolled; age range, 1–17 years).¹⁹⁹ The efficacy analysis included 104 patients, who all achieved CR; 15 of the patients received allogeneic HSCT in CR1. An interim analysis showed a 3-year EFS of 66.0% (95% CI, 54.8%–75.0%) and a 3-year OS of 92.3% (95% CI, 85.2%–96.1).¹⁹⁹

St. Jude Total Therapy XV–XVII Studies

In the Total XVI study from the St. Jude Children's Research Hospital, Jeha et al sought to compare the response rates and overall clinical outcome of pediatric patients with Ph-positive ALL treated in the pre-TKI era versus with the current approach of incorporating a TKI.²⁰⁰ Patients with newly diagnosed B-ALL ($n=1035$; age range, 1–18 years) were treated on low- and standard-/high-risk arms, including 30 patients with Ph-positive ALL.²⁰⁰ The TKIs, imatinib or dasatinib were administered

continuously through all phases of treatment starting on days 22 through 26 of remission induction therapy, and resulted in significant reductions in MRD when compared with the pre-TKI cohort that received chemotherapy alone ($P<.001$).²⁰⁰ The 5-year EFS for the TKI versus pre-TKI groups was $68.6\pm 19.2\%$ and $31.6\pm 9.9\%$, respectively ($P=.022$).²⁰⁰ In the Total XVII study, dasatinib will be given to patients with Ph-positive ALL and patients with ABL-class chimeric fusions (ie, involving *ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, or *PDGFRB*) identified by RNA-Seq.⁷⁴ In this setting, dasatinib will be given on day 15 of remission induction.⁷⁴

Hematopoietic Stem Cell Transplant

A retrospective analysis by Aricò et al²⁰¹ reported significant improvement in 5-year DFS and OS for pediatric and AYA patients with Ph-positive ALL in CR1 who received HSCT, including matched related donor, matched URD, or mismatched related donor allogeneic SCT or autologous SCT, versus those who received chemotherapy alone without TKIs.¹⁹⁸ In the large, international, collaborative MRC UKALL XII/ECOG E2993 trial conducted in patients with previously untreated ALL, the subgroup with Ph-positive disease ($n=267$; median age, 40 years; range, 15–60 years) was eligible for allogeneic HSCT if patients were younger than 50 (in the ECOG E2993 trial) or 55 (in the MRC UKALL XII trial) years of age and had a matched sibling or matched URD.²⁰² Among the Ph-positive patient cohort, postremission treatment included matched sibling allogeneic HSCT ($n=45$), matched URD allogeneic HSCT ($n=31$), and chemotherapy alone ($n=86$). The 5-year OS rate according to postremission therapy was 44%, 36%, and 19%, respectively, and the 5-year EFS rate was 41%, 36%, and 9%, respectively.²⁰² Both the OS and EFS outcomes for patients who underwent allogeneic HSCT (related or unrelated) were significantly improved compared with those who received only chemotherapy. The incidence of transplant-related mortality was 27% with matched sibling allogeneic HSCT and 39% with matched URD HSCT. An intent-to-treat analysis of patients with a matched sibling donor versus those without a matched sibling donor showed no statistically significant difference in 5-year OS rates (34% vs 25%, respectively).²⁰²

As mentioned earlier, the COG AALL0031 trial reported similar 3-year EFS rates among very high-risk patients with Ph-positive ALL in CR1 who received imatinib with intensive chemotherapy followed by HSCT or those who received chemotherapy with imatinib maintenance without HSCT.^{128,129,198}

Management of Patients With Relapsed or Refractory Ph-Positive ALL

As previously mentioned, the outcomes of pediatric patients with R/R B-ALL has been historically poor.

In Ph-positive ALL, several mechanisms may contribute to this including the development of resistance to TKIs.⁵⁴ Several trials referenced in the algorithm have developed regimens that are currently used to treat R/R Ph-positive B-ALL, and these studies are summarized subsequently.

Chemotherapy and Tyrosine Kinase Inhibitors

In a phase I study, the efficacy and toxicity of imatinib was evaluated in pediatric patients with R/R Ph-positive leukemia, including cases of ALL, AML, and chronic myeloid leukemia (n=31).²⁰³ In this study, imatinib demonstrated a good toxicity profile and was well tolerated at doses ranging from 260 to 570 mg/m²/day. Among patients with ALL evaluable for morphologic response (n=10), 7 achieved an M1 and 1 achieved an M2 bone marrow.²⁰³ In the COG AALL0031 study, pediatric patients with Ph-positive ALL who relapsed after initial treatment with imatinib and chemotherapy were able to achieve an overall CR2 rate of 67% (n=20/30).¹²⁹ Of the patients who attained CR2, 85% (n=17/20) remained in remission for at least 3 months.¹²⁹

Blinatumomab

An open-label, single-arm, multicenter, phase II study evaluated the efficacy and safety of blinatumomab in adult patients (aged ≥18 years) with R/R Ph-positive ALL who had progressed after imatinib and at least one second- or third-generation TKI (n=45).²⁰⁴ During the first 2 cycles of blinatumomab, 36% achieved complete remission or complete remission with partial hematologic recovery, and 88% of these responders achieved a complete MRD response.²⁰⁴ In July 2017, blinatumomab received full approval from the FDA for the treatment of R/R precursor B-cell ALL (Ph-negative and Ph-positive) and clinical studies described earlier include patients with R/R Ph-positive and Ph-negative ALL.^{134,149–151} Several adult studies have tested the combination of blinatumomab and a TKI.^{204,205} For discussion of these studies, see “Management of Patients with Relapsed or Refractory Ph-Negative or Ph-Like ALL” (page 96).

CAR T Cells

Clinical studies described earlier include patients with R/R Ph-positive and Ph-negative ALL.^{136,185,186,189} For discussion of these studies, see “Management of Patients with Relapsed or Refractory Ph-Negative or Ph-Like ALL” (page 96).

Inotuzumab Ozogamicin

Clinical studies described earlier include patients with R/R Ph-positive and Ph-negative ALL.^{194–196} For discussion of

these studies, see “Management of Patients with Relapsed or Refractory Ph-Negative or Ph-Like ALL” (page 96).

Hematopoietic Stem Cell Transplant

As mentioned previously, the American Society for Transplantation and Cellular Therapy guidelines recommend HSCT for pediatric patients with ALL in CR2 after experiencing an early marrow relapse.¹⁹⁸ Treatment options are extremely limited for patients with Ph-positive ALL who experience relapse after receiving consolidation with allogeneic HSCT. Some studies have reported on the feasibility of inducing a second molecular CR with TKIs including imatinib and dasatinib in those who have experienced an early relapse after first allogeneic HSCT, which allowed for a second allogeneic HSCT.^{206–208}

NCCN Recommendations for Ph-Positive ALL

Front-line Management

The panel recommends that pediatric and AYA patients with Ph-positive ALL be treated in a clinical trial that incorporates TKIs when possible (see PEDALL-5, page 87). In the absence of an appropriate clinical trial, patients are treated with chemotherapy and a TKI (see PEDALL-5, page 87). After a response assessment, standard-risk patients (ie, low MRD) continue consolidation chemotherapy and maintenance therapy with a TKI. As an alternative for maintenance, HSCT may be considered. In patients who are high risk (ie, less than CR, MRD+ at the end of consolidation, or high-risk genetics) after induction therapy, additional options include blinatumomab and tisagenlecleucel (category 2B recommendation). In these patients, consolidation with HSCT is recommended and posttransplant TKI should be considered. Of note, HSCT is not required but may be considered for Ph-positive ALL in CR1.

R/R Management

The NCCN Panel recommendations for pediatric and AYA patients with R/R Ph-positive ALL are similar to what has been summarized for R/R Ph-negative or Ph-like ALL (see PEDALL-9, page 91, and PEDALL-11, page 93). If feasible, *BCR-ABL1* kinase domain mutation analysis (eg, T315I) should be performed and appropriate TKI should be added to the regimen.

Management of T-ALL

T-ALL is biologically distinct from B-ALL; however, similar to B-ALL, MRD is a key prognostic determinant.⁸³ A major theme in current T-ALL treatment approaches is early intensification with multiagent chemotherapy followed by intensive consolidation therapy. Based on trials

referenced in the algorithm, the management of de novo T-ALL is summarized below.

Front-line Management of Patients With T-ALL

COG AALL0434

Nelarabine is a nucleoside metabolic inhibitor and a prodrug of ara-G, approved for the treatment of patients with T-ALL with disease that has not responded to or that has relapsed after at least two chemotherapy regimens. The randomized phase III COG study (AALL0434) evaluated the safety of nelarabine as part of frontline therapy, using the augmented BFM chemotherapy regimen, with or without nelarabine, and showed that the toxicity profiles were similar between patients with high-risk T-cell ALL who received nelarabine ($n=47$) and those who did not ($n=47$).²⁰⁹ No significant differences were observed in the occurrence of neurologic adverse events between these groups, including peripheral motor neuropathy, peripheral sensory neuropathy, or CNS neurotoxicity. The incidence of adverse events such as febrile neutropenia and elevation of liver enzymes was also similar between treatment groups. These initial safety data suggest that nelarabine may be better tolerated in frontline regimens than in the R/R setting.²⁰⁹

Results from the efficacy phase of this study evaluated data from 1,895 patients with newly diagnosed T-ALL and T-cell lymphoblastic leukemia.²¹⁰ Patients were randomized to receive escalating-dose methotrexate without leucovorin rescue and PEG or high-dose methotrexate with leucovorin rescue. Intermediate- and high-risk patients with T-ALL and T-cell lymphoblastic leukemia all received prophylactic or therapeutic cranial irradiation and were randomized into arms with or without nelarabine (650 mg/m²/day). The 4-year DFS rate for patients with T-ALL in the nelarabine arm ($n=323$) versus those who did not receive nelarabine ($n=336$) was 88.9%±2.2% and 83.3%±2.5%, respectively ($P=.0332$).²¹⁰ For patients randomized to receive high-dose methotrexate, the addition of nelarabine appeared to enhance the 4-year DFS rate: no nelarabine, 78.0%±3.7% versus with nelarabine, 86.2%±3.2%; $P=.024$.²¹⁰

Another report from the COG AALL0434 study investigated the impact of 2 different approaches to methotrexate intensification on pediatric T-ALL outcomes.⁸⁶ All patients without CNS3 disease or testicular leukemia were randomized to receive an augmented BFM chemotherapy regimen with either C-MTX ($n=519$) or HD-MTX ($n=512$) during the 8-week IM phase.⁸⁶ The estimated 5-year DFS and OS rates in the C-MTX group were significantly higher than observed in the HD-MTX group, at 91.5% vs 85.3%, respectively ($P=.005$) and 93.7% vs 89.4%, respectively ($P=.04$).⁸⁶ These data demonstrate that C-MTX combined with chemotherapy

is superior to HD-MTX and chemotherapy in patients with T-ALL.⁸⁶

DFCI ALL Consortium Protocol 05-001

In the DFCI ALL Consortium Protocol 05-001, pediatric patients (aged 1–18 years) with newly diagnosed T-ALL were treated as high risk regardless of other presenting features ($n=97$).⁸⁵ With a median follow-up of 4.3 years, the 4-year EFS and OS rates were 83% and 89%, respectively. EOI MRD, assessed by PCR, was evaluable in 58 (67%) patients who achieved CR, and high MRD was associated with inferior DFS.⁸⁵

Hematopoietic Stem Cell Transplant

In a retrospective analysis of the ALL BFM 90 and 95 trials evaluating the impact of chemotherapy alone versus allogeneic HSCT in pediatric patients with T-ALL, Schrauder et al²¹¹ reported a significant improvement in 5-year DFS and OS with allogeneic HSCT versus chemotherapy alone in CR1. However, HSCT in CR1 is not indicated in the contemporary protocols unless MRD is positive.

Management of Patients With Relapsed or Refractory T-ALL

Most T-ALL disease recurs within 2 years of diagnosis, and successful remission induction is a significant challenge in R/R T-ALL.⁸³ Based on trials referenced in the algorithm, the management of R/R T-ALL is summarized subsequently.

Nelarabine-Based Regimens

Nelarabine is a nucleoside analog that is currently approved for the treatment of patients with T-ALL who have unresponsive or relapsed disease after at least 2 chemotherapy regimens. A phase II study of nelarabine monotherapy in children and adolescents with R/R T-ALL or T-cell non-Hodgkin's lymphoma ($n=121$) showed a 55% response rate among the subgroup with T-ALL with first bone marrow relapse ($n=34$) and a 27% response rate in the subgroup with a second or greater bone marrow relapse ($n=36$).¹³² Major toxicities included grade 3 or higher neurologic (both peripheral and CNS) adverse events in 18% of patients. Nelarabine as single-agent therapy was also evaluated in AYAs and adults (≥ 16 years of age) with R/R T-ALL or T-cell lymphoblastic lymphoma in a phase II study ($n=39$; median age, 34 years; range, 16–66 years; median 2 prior regimens; T-ALL, $n=26$).²¹² The CR rate (including CRi) was 31%; an additional 10% of patients experienced a partial remission. The median DFS and OS were both 20 weeks and the 1-year OS rate was 28%. Grade 3 or 4 myelosuppression was common, but only one case of grade 4 CNS toxicity (reversible) was observed.²¹²

In a phase I trial, NECTAR, the efficacy and safety of nelarabine in combination with etoposide and cyclophosphamide was evaluated in children with R/R T-ALL

or T-cell lymphoblastic lymphoma (n=19).²¹³ Of evaluable patients with R/R T-ALL (n=9), a 44% response rate was observed.²¹³

Bortezomib-Based Regimens

The referenced study, COG AALL07P1, evaluating a bortezomib-containing regimen included pediatric patients with R/R T-ALL.¹⁶³ For a summary, refer to “Management of Patients with Relapsed or Refractory Ph-negative or Ph-like ALL” (page 96).

UKALL R3

The referenced study, UKALL R3, evaluating the effect of mitoxantrone in multiple risk-stratified chemotherapy blocks included pediatric patients with R/R T-ALL.^{157,159} For a summary, refer to “Management of Patients with Relapsed or Refractory Ph-negative or Ph-like ALL” (page 96).

ALL-REZ BFM 90

The referenced study, ALL-REZ BFM 90, evaluating risk-stratified multichemotherapy blocks, included pediatric patients with R/R T-ALL.¹⁶⁰ For a summary, refer to “Management of Patients with Relapsed or Refractory Ph-negative or Ph-like ALL” (page 96).

Hematopoietic Stem Cell Transplant

HSCT is the only curative treatment of R/R T-ALL, but this requires successful remission induction and the data are limited.⁸³ In the COG AALL01P2 study, most patients with T-ALL (n=5 of 7) did not experience CR2.¹⁶¹ In the MRC UKALL R1 trial, compared with chemotherapy alone, allogeneic HSCT did not significantly improve EFS in pediatric patients with R/R ALL.²¹⁴

NCCN Recommendations for T-ALL

Front-line Management

The panel recommends that pediatric and AYA patients with T-ALL be treated in a clinical trial when possible. In the absence of an appropriate clinical trial, patients are treated with chemotherapy (see PEDALL-6, page 88). After a response assessment, standard- or high-risk patients continue consolidation chemotherapy. The features that define standard risk in this context are: day 29 MRD <0.01%, CNS-1, absence of testicular disease, and no steroid pretreatment. Very-high-risk patients have end of consolidation MRD >0.1%. High-risk patients in this context do not exhibit any standard- or very high risk factors. Patients who have very high risk features may continue chemotherapy or pursue alternative therapy and consider HSCT as part of consolidation therapy. However, it is recommended that additional therapy be given to achieve MRD negativity before HSCT.

R/R Management

For pediatric and AYA patients with T-ALL experiencing first relapse, the panel recommends initial treatment with clinical trial or chemotherapy (see PEDALL-10, page 92). If patients experience CR2, consolidation therapy with chemotherapy should be continued with HSCT. If patients experience less than CR (ie, multiple relapse), treatment options include chemotherapy, and patients may receive HSCT as consolidation therapy if they subsequently respond to therapy (see PEDALL-11, page 93). If the disease does not respond to therapy, alternative treatment options may be considered with best supportive and palliative care (see PEDALL-11, page 93).

Management of Infant ALL

Most infant patients with ALL present with aggressive features, including high WBC counts, CNS involvement, and leukemia cutis, necessitating the use of intensive chemotherapy regimens.³⁴ However, infant patients are especially vulnerable to treatment-related toxicities, so clinical trials are continually investigating novel strategies to reduce this.³⁴ Based on trials referenced in the algorithm, the management of infant ALL is summarized in subsequent sections.

Front-line Management of Infants With ALL

Interfant-99

In a multicenter Interfant-99 trial, 482 infant patients with ALL, aged 0 to 12 months, were risk-stratified according to peripheral blood response to a 7-day prednisone prophase, and treated with a hybrid protocol that incorporated elements of standard ALL and AML regimens.³⁶ Response was defined as good, and risk as standard, if the blast count in peripheral blood at day 8 was <1000 cells/ μ L. A poor response was defined as a blast count \geq 1000 cells/ μ L at day 8.³⁶ High-risk patients were eligible to receive HSCT at the end of the reinduction phase if a donor was available. At the EOI, 94% of 474 evaluable patients were in complete remission (312 standard risk patients and 133 high-risk patients).³⁶ At a median follow-up of 38 months (range, 1–78 months), 58% of patients (n=260) who underwent hybrid treatment were in complete remission and the 4-year EFS was 47%. High WBC count, age <6 months, a poor response to the prednisone prophase, and *KMT2A* rearrangements were all independently associated with inferior outcomes.³⁶ In addition, before the maintenance phase, a subset of patients in CR were randomly assigned to receive either standard treatment or more intensive chemotherapy with high-dose cytarabine and methotrexate, which did not improve outcomes.³⁶

Interfant-06

In infant ALL, the immature B-cell precursors frequently coexpress myeloid markers and are sensitive to

cytarabine, a key drug in AML treatment.^{9,215,216} Based on the hypothesis that early hematopoietic precursors with myeloid differentiation potential would elicit improved responses to chemotherapy regimens developed for AML,³⁴ the Interfant-06 trial investigated whether consolidation with myeloid-style chemotherapy was superior to lymphoid-style chemotherapy in infant patients with ALL (n=651).⁹ In the study, 3 risk groups were defined: low risk (*KMT2A* germline; n=167); high risk (*KMT2A*-rearranged and >6 months with WBC count $\geq 300 \times 10^9/L$ or poor prednisone response; n=164); and medium-risk (all other *KMT2A*-rearranged cases; n=320). Patients in the medium- and high-risk groups were randomly assigned to receive a lymphoid consolidation course (low-dose cytarabine, 6-MP, and cyclophosphamide [IB]) or experimental myeloid courses (cytarabine, daunorubicin, and etoposide [ADE]; and mitoxantrone, cytarabine, and etoposide [MAE]). The 6-year EFS and OS probabilities of all patients were 46.1% and 58.2%, respectively.⁹ The 6-year probability of DFS was comparable for the randomized arms (ADE+MAE 39.3% vs IB 36.8%; log-rank $P=.47$).⁹

COG AALL0631

Based on data showing aberrant activation of *FLT3* pathway in infant ALL with *KMT2A* rearrangements,^{217–219} the COG AALL0631 trial was designed to evaluate whether the addition of a *FLT3* TKI, lestaurtinib, to postinduction chemotherapy would increase treatment efficacy in infants with newly diagnosed ALL.^{34,220} Initial induction consisted of 3 weeks of therapy based on a COG P9407 backbone (cohort 1).^{220,221} Differences between the revised COG P9407 induction and the AALL0631 induction included use of low-dose cytarabine instead of cyclophosphamide, decreased daunorubicin dose and substitution of native L-asparaginase with pegaspargase.²²⁰ Due to excessive induction toxicity, the study was amended to include a modified 5-week Interfant-99 based induction and enhanced supportive care guidelines (cohort 2).²²⁰ Induction mortality and sterile site infections were significantly lower for patients in cohort 2, and higher complete response rates were observed at the end-induction intensification for cohort 2 (week 9, n=94/100 [94%]) versus cohort 1 (week 7, n=17/25 [68%]; $P=.0012$).²²⁰ The addition of lestaurtinib did not demonstrate a benefit in outcomes.³⁴

Hematopoietic Stem Cell Transplant

The benefit derived from using HSCT in infant leukemia is unclear.³⁴ Several retrospective studies suggest no clinical advantage or a benefit at low EFS rates.²²² In the Interfant-99 study, only a subgroup of infant patients with *KMT2A*-rearranged ALL and additional poor prognostic factors (age <6 months, poor response to steroids

at day 8, high WBC) appeared to benefit from HSCT in CR1 over chemotherapy alone.¹²⁵

Management of Infant Patients With Relapsed or Refractory ALL

Infant patients with R/R ALL have poor outcomes, and few studies have focused on this specific group.^{223,224} Studies summarized previously for B-ALL and T-ALL include some infant patients, and those management strategies apply in this context.

NCCN Recommendations for Infant ALL

Front-line Management

The panel recommends that infant patients with ALL be treated in a clinical trial when possible. In the absence of an appropriate clinical trial, patients are treated with Interfant-based chemotherapy (see PEDALL-7, page 89). To ensure appropriate consolidation, it is important to assess the *KMT2A* status of the disease. If the patient is standard-risk (ie, *KMT2A* not rearranged), after a response assessment, the patient may be treated with Interfant-based consolidation. Alternatively, patients who are MRD negative after induction will continue risk-stratified chemotherapy similar to what has been described for Ph-negative or Ph-like ALL. Patients who are MRD positive after induction may undergo intensified consolidation therapy. In all cases, HSCT may be considered as part of consolidation or maintenance therapy (see PEDALL-7, page 89).

If the patient has *KMT2A* rearranged, he or she is treated with an intensive Interfant-based consolidation chemotherapy. If the patient is high risk (ie, aged <3 months with any WBC, aged <6 months with WBC $\geq 300,000$, or persistently MRD+ after intensive consolidation therapy), maintenance therapy is recommended or HSCT may be considered. If a donor is available, it is preferred that a non-total body irradiation-based prep regimen is used and the patient is at least 6 months at the time of transplant. If the patient is intermediate-risk (ie, does not have any high-risk features), maintenance chemotherapy is recommended (see PEDALL-7, page 89).

R/R Management

The NCCN Panel recommendations for infant patients with R/R ALL are similar to what has been summarized for R/R Ph-negative or Ph-like ALL (see PEDALL-9, page 91, and PEDALL-11, page 93).

Surveillance

After completion of the ALL treatment regimen (including maintenance therapy), the panel recommends surveillance at regular intervals to assess disease status

(see PEDALL-8, page 90). During the first year after completion of therapy, every 1 to 4 months, patients should undergo a complete physical examination (including a testicular examination as applicable) and blood tests (CBC with differential). Liver function tests should be performed until normal values are achieved. During the second year after completion of therapy, a physical examination (including a testicular examination as applicable) and blood tests (CBC with differential) should be performed every 3 to 6 months. During the third year (and beyond) after completion of therapy, physical examination (including a testicular examination as applicable) and blood tests (CBC with differential) can be performed every 6 to 12 months or as clinically indicated.

An assessment of bone marrow aspirate and colony-stimulating factor for suspected relapse should be performed as clinically indicated; if a bone marrow aspirate is performed, flow cytometry with additional studies that may include comprehensive cytogenetics, FISH, molecular tests, and MRD assessments should be performed. If relapse is suspected, a full workup should be considered. For Ph-positive ALL, periodic quantification of the *BCR-ABL1* transcript should be determined.

To monitor for late effects related to cumulative anthracycline exposure, an echocardiogram should be performed as clinically indicated. In addition, given the increased risk of neurotoxicity associated with ALL treatment in survivors, neuropsychological testing as clinically indicated is recommended. Patients with a history of pediatric ALL are also at risk for developing obesity,²²⁵ therefore, monitor for healthy weight and encourage healthy lifestyle choices. Further recommendations for survivorship are available in the NCCN Guidelines for

AYA Oncology and NCCN Guidelines for Survivorship (available at NCCN.org). In addition, the COG has published guidelines on long-term survivorship issues for survivors of childhood cancers.²²⁶ These guidelines serve as a resource for clinicians and family members/caretakers, and have the goal of providing screening and management recommendations for late effects (those that may impact growth, cognitive function, emotional concerns, reproductive health, risks for secondary malignancies, and other important health issues) that may arise during the lifetime of an AYA cancer survivor as a result of the therapeutic agents used during the course of antitumor treatment.

Summary of Principles of Pediatric ALL Treatment

Current management of pediatric ALL is divided into induction chemotherapy, consolidation therapy, maintenance, CNS prophylaxis, and HSCT. The treatment strategy is influenced by individual patient characteristics such as age, WBC count, immunophenotypic/cytogenetic/genetic subtype, presence of CNS disease, and response to induction therapy. With a strong correlation between MRD and risk of relapse, and prognostic significance of MRD measurements during and after induction therapy, MRD testing in pediatric ALL is an essential part of patient evaluation and disease management. Improved cure rates in pediatric ALL have generated a large group of long-term survivors who are at risk for treatment-related complications and who require surveillance and appropriate interventions to manage short-term and late effects. Consistent with NCCN philosophy, participation in clinical trials is always strongly encouraged.

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Individual Disclosures for the NCCN Pediatric Acute Lymphoblastic Leukemia Panel

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