**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.

**NCCN CATEGORIES OF EVIDENCE AND CONSENSUS**

- **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.
- **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

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.

**PLEASE NOTE**

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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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**Disclosures for the NCCN Pediatric Acute Lymphoblastic Leukemia Panel**

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself. 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.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.
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, with approximately 5,930 new cases and 1,500 deaths estimated in 2019. It is also the most common pediatric malignancy, representing 75%–80% of acute leukemias among children. The median age at diagnosis for ALL is 15 years, with 55.4% of patients diagnosed at younger than 20 years of age. 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.

The cure rates and survival outcomes for pediatric patients with ALL have improved dramatically over the past several decades. 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. 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. 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%.

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. The NCCN Guidelines 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

8 The 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 Leukemia8 are intended to be applied to AYA patients treated in an adult oncology setting.

9 Subtypes: B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities includes hyperdiploidy, hyperdiploidy, and commonly occurring translocations: t(9;22)(q34.1;q11.2), t(11;22)(q23.1;q12.2), t(4;11)(q21.3;p15.1), t(1;19)(p13.2;q13.3), t(1;19)(p13.2;q13.3). Early detection of these abnormalities requires the use of a fluorescent in situ hybridization (FISH) assay. A minority of patients with ALL (1-5%) present with chromosome 1q22 deletion (1q22del). The patient who has this deletion may present with an excess of blasts (EOB) in the bone marrow aspirate (Eob >10%). The EOB in the bone marrow aspirate is typically absent in pediatric ALL. The presence of a deletion of 1q22 in a patient with ALL should prompt a karyotype analysis and/or FISH assay of the bone marrow aspirate.

10 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.

11 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 testes).4 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% blasts is often used in treatment protocols to define leukemia.14,15 Peripheral blood may be substituted for bone marrow provided there is a significant amount of circulating disease,15 with the NCCN Pediatric ALL Panel suggesting a general guide of ≤1,000 circulating lymphoblasts per microliter or ≥20% lymphoblasts.
The 2016 WHO classification lists ALL and lymphoblastic lymphoma as the same entity, distinguished only by the primary location of the disease.\(^1\)\(^,\)\(^1\)\(^4\)\(^,\)\(^1\)\(^7\) 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.\(^1\)\(^4\)\(^,\)\(^1\)\(^7\) 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\(^1\)\(^8\)\(^,\)\(^1\)\(^9\) 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.\(^2\)\(^0\) 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 \((BCR-ABL1–like \text{ALL} \text{ or Ph-like ALL})\)\(^2\)\(^\text{1}\)\(^,\)\(^2\)\(^2\) and B-lymphoblastic leukemia/lymphoma with intrachromosomal amplification of chromosome 21 \((iAMP21)\).\(^2\)\(^1\)\(^,\)\(^2\)\(^3\) Two new provisional entities were also added to T-ALL: early T-cell precursor lymphoblastic leukemia and natural killer cell lymphoblastic leukemia/lymphoma.\(^2\)\(^1\)

In these guidelines, the NCCN Panel for Pediatric ALL has delineated the features that are commonly associated
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 age of 10–11 years.42,43

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RISK STRATIFICATION

INDUCTION THERAPY†

CONSOLIDATION THERAPY

MRD±

See PEDALL-4

MRD-

Continue risk-stratified therapy±,±x

Maintenance therapy±,±x

See Surveillance (PEDALL-8)

High risk±

Clinical trial or Chemotherapy±

Response Assessment (PEDALL-H*)

MRD±

See PEDALL-4

MRD-

Continue risk-stratified therapy±,±x

Maintenance therapy±,±x

See Surveillance (PEDALL-8)

Ph-negative or Ph-like B-ALL±

Standard risk±

Clinical trial or Chemotherapy±

Response Assessment (PEDALL-H*)

†For patients with Down syndrome, see Special Considerations for Vulnerable Populations (PEDALL-D*).
††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*).
†††See Principles of Supportive Care (PEDALL-L-E†††).
††††See Principles of Systemic Therapy (PEDALL-E††††).
‡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-F†††‡).
§For Ph-like patients, TKIs may be considered. For more information see Principles of Systemic Therapy (PEDALL-F§).

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

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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-ALL57,48 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.93,50 An analysis of the MRD-dependent prognostic impact of IKZF1 deletions with co-occurring deletions in CDKN2A, CDKN2B, PAX5, or PAR1 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, PDGFRα, 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,
**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**. 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. In patients with T-ALL, **NOTCH1** and **FBXW7** mutations have generally been associated with favorable prognosis and lower MRD levels. 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.

**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 (i.e., 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). **Low-density arrays**, **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 **PTK2B** genes. 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.
FGFR1 rearrangements. 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
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. Importantly, children with Down syndrome are at an increased risk for the development of ALL. 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. 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 × 10⁹ cells/L, whereas all other patients with ALL, including T-ALL (regardless of age or WBC count), were considered high risk.

Different cooperative groups have used a combination of clinical, biologic, and response variables to allocate patients into risk groups based on outcome.
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); BCR-ABL1–like or Ph-like ALL; patients younger than age 1 with KMT2A gene rearrangement; and failure to achieve remission with induction therapy. Conversely, criteria were refined for lower risk and included patients with hyperdiploidy, especially with simultaneous trisomies of chromosomes 4, 10, and 17, and the t(12;21) chromosomal translocation (ETV6-RUNX1 subtype). 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. 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. The COG 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. In the United States, other groups have also developed standards for risk-stratiﬁed treatment approaches, including the St. Jude Consortium and the Dana-Farber Cancer Institute (DFCI) ALL Consortium. 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.

COG Approach
In the COG approach, patients with B-ALL are initially classiﬁed as standard risk (ie, aged 1 to <10 years and WBC
count \(<50\times10^9\) cells/L) or high risk (ie, aged \(\geq 10\) years and/or WBC count \(>50\times10^9\) 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]).\(^8\) After induction, a critical measure used to ascribe risk is MRD,\(^8\) 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 \(0.1\%\) to \(0.01\%\), and peripheral blood MRD is assessed at day 8 instead of day 8/day 15 bone marrow aspirates for morphology.\(^8\) 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.\(^8\) For patients requiring an end of consolidation MRD assessment, the threshold between intermediate and very high risk is \(\geq 0.1\%).\(^8\)

**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 \(\geq 1.16\) and having the \(ETV6-RUNXI\) fusion, or B-ALL with age 1–9.9 years and WBC count \(<50\times10^9\) cells/L, or if they lack standard-risk features. Patients with standard-risk features include: B-ALL patients aged \(\geq 10\) years or presenting with WBC count \(\geq 50\times10^9\) cells/L (not including DNA index \(\geq 1.16\) or the presence of the \(ETV6-RUNXI\) fusion); B-ALL patients with CNS-3 status, overt testicular leukemia, or adverse genetic features including \(BCR-ABL1\) fusion/\(t(9;22)\), \(TCF3-PBXI\) fusion/\(t(1;19)\), \(KMT2A\) rearrangement, hypodiploidy, \(iAMP21\), or \(MEF2D\) fusion; or if the patients have T-ALL.\(^8\) 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 (\(\geq 0.1\%\) 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.\(^9\) The initial grouping includes: standard risk (ie, aged 1 to \(<15\) years, WBC count \(<50\times10^9\) cells/L, and lacking high-risk or very-high-risk adverse biologic features); high risk (ie, disease expressing \(BCR-ABL1\) and
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)]. 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. 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). 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.

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. The observed advantage in outcomes with dexamethasone may partly be attributed to improved penetration of...
Dexamethasone into the CNS. 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, 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.

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. Erwinia asparaginase is typically given to patients who have experienced an allergic reaction to pegaspargase, and it requires a more frequent administration schedule. 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.

**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. 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.

**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.\textsuperscript{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.\textsuperscript{110,111} Furthermore, age, gender, and genetic polymorphisms can affect bioavailability.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{119} Quantification of 6-MP metabolites can be very useful in determining whether the lack of myelosuppression is due to noncompliance 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, 1-Asparaginase).\textsuperscript{87,95,97,105,129} 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 should be treated with cranial irradiation and, in R/R disease settings.

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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{131} The purine nucleoside analog nelarabine has been approved for the treatment of R/R T-ALL or lymphoblastic lymphoma.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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,
vindristine, 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). At the EOI, patients were randomized to receive standard consolidation (6-MP, vindristine, and intrathecal methotrexate) versus intensified consolidation (cyclophosphamide, cytarabine, 6-MP, vindristine, pegaspargase, and intrathecal methotrexate). 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. 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% an 94%, respectively.

Due to the intensification of premaintenance therapy and modern risk stratification, 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 vindristine 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. The 5-year DFS (± standard error) for the average risk patients randomized to receive vindristine and dexamethasone pulses every 4 weeks versus every 12 weeks was 94.1% ± 1.0% vs 95.1% ± 0.9% (one-sided P=.86).

**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. 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 AALL0232 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.

Relative to pediatric patients with standard risk B-ALL, patients with high-risk B-ALL experience high relapse rates and worse clinical outcomes. 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. Patients enrolled on this trial received a standard 4-drug induction (dexamethasone/prednisone, vindristine, 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. 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. 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), 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). 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. At study entry, patients were classified as standard risk or high risk and a 4-drug induction was used (prednisone, vindristine, doxorubicin, and pegaspargase). 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. 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. 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 ≥15 years of age had a significantly worse outcome. 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.

**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. 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. This study demonstrated that prophylactic cranial irradiation could be omitted without compromising OS.

The ongoing Total XVI Study will incorporate novel precision medicine strategies based on genomic features and targeted treatment. 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.

**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. 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 al 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 ≥10⁻⁴. After blinatumomab treatment, 16 of 20 evaluable patients were determined to be MRD-negative at a detection threshold of 10⁻⁴. After a median follow-up of 33 months, the hematologic recurrence-free survival of the evaluable cohort was 61%. Gökbüget et al 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 ≥10⁻¹). 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%. 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. 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 ≥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. 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. 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. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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%).\textsuperscript{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 \textit{P}<.001.\textsuperscript{160} Significant predictors of EFS in multivariate analyses included time point, site of relapse, immunophenotype, and HSCT.\textsuperscript{180}

**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).\textsuperscript{161} Patients with CNS leukemia were non-randomly assigned to arm A to allow early introduction of high-dose cytarabine, and patients with mature B-ALL and Down syndrome were excluded.\textsuperscript{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% (\textit{P}<.0001), respectively.\textsuperscript{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.\textsuperscript{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). 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.\textsuperscript{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 (≥10\textsuperscript{-4} cells) received HSCT. The estimated 3-year PFS and OS rates in the mitoxantrone versus idarubicin groups were 64.6% versus 35.9% (\textit{P}=0.004); and 69% versus 45.2% (\textit{P}=0.004), respectively.\textsuperscript{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.\textsuperscript{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\textsuperscript{-4} cells; \textit{P}=0.007).\textsuperscript{157}

**COG AALL07P1**

Bortezomib is a proteasome inhibitor that has demonstrated some activity in relapsed pediatric ALL.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{170–173} In a study by Gabriel et al,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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).\textsuperscript{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.\textsuperscript{156,177} 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).\textsuperscript{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=0.01).\textsuperscript{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).\textsuperscript{149} Of note, prespecified subgroup analyses of patients with high bone marrow count (≥50%) at relapse demonstrated lower blinatumomab-mediated median survival and remission rates.\textsuperscript{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.\textsuperscript{149} Based on phase I data, the recommended dosage of blinatumomab was 5 µg/m\textsuperscript{2}/day for the first 7 days, followed by 15 µg/m\textsuperscript{2}/day afterward.\textsuperscript{149} 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.\textsuperscript{149}

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.\textsuperscript{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.\textsuperscript{178} CRS typically occurs within the first 2 days after start of blinatumomab infusion.\textsuperscript{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-host 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. 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. The CAR T cell therapy relies on the genetic manipulation of a patient's T cells to generate a response against a leukemic cell-surface antigen, most commonly CD19. 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. 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. 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. In addition, 7 of 16 patients were able to receive an allogeneic HSCT, suggesting that CAR T cells may provide a bridge to transplant. 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. 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). 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.

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. 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. There was no response of the disease to treatment in 3 patients and disease response to therapy was still under evaluation for 3 patients. 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. 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. 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. 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.

Several groups have developed comprehensive guidelines regarding grading systems for and management of CAR T-cell–associated toxicities. Inotuzumab Ozogamicin

Inotuzumab ozogamicin (InO) is a calicheamicin-based antibody-drug conjugate targeting CD22. Following the generation of encouraging single-agent phase II data, 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). Notably, responses were consistent across most subgroups, including those with high marrow burden, and those with Ph-positive leukemias. 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). 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%). 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.

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. At 3 years, OS rates were 16% (95% CI, 13%–20%). 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.

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. 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. 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). 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). 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. Subsequent follow-up after 5 years confirmed these outcomes. 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. The 5-year OS and EFS rates (± SD) were 86% ± 5% and 60% ± 7%, respectively, and outcomes were similar to those observed in COG AALL0031.

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. 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 statistically different between the 2 groups (P = .64). 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. 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. 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). 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%).

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. 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. 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). The 5-year EFS for the TKI versus pre-TKI groups was 68.6 ± 19.2% and 31.6 ± 9.9%, respectively (P = .022). In the Total XVII study, dasatinib will be given to patients with Ph-positive ALL and patients with ABL1-class chimeric fusions (ie, involving ABL1, ABL2, CSF1R, PDGFRα, or PDGFRβ) identified by RNA-Seq. In this setting, dasatinib will be given on day 15 of remission induction.

Hematopoietic Stem Cell Transplant
A retrospective analysis by Aricò et al 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. 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. 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. 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).

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.

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. 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 \( n = 31 \). In this study, imatinib demonstrated a good toxicity profile and was well tolerated at doses ranging from 260 to 570 mg/m\(^2\)/day. Among patients with ALL evaluable for morphologic response \( n = 10 \), 7 achieved an M1 and 1 achieved an M2 bone marrow. 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% \( n = 29/40 \). Of the patients who attained CR2, 85% \( n = 17/20 \) remained in remission for at least 3 months.

**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 \( n = 45 \). 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. 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. Several adult studies have tested the combination of blinatumomab and a TKI. 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. 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. 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. 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.

**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. A major theme in current T-ALL treatment approaches is early intensification with multiagent chemotherapy followed by intensive consolidation therapy. Based on trials...
referred 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=523) 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/μL. A poor response was defined as a blast count ≥1000 cells/μL at day 8.36 High-risk patients were eligible to receive HSCT at the end of the induction 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. Based on the hypothesis that early hematopoietic precursors with myeloid differentiation potential would elicit improved responses to chemotherapy regimens developed for AML, the Interfant-06 trial investigated whether consolidation with myeloid-style chemotherapy was superior to lymphoid-style chemotherapy in infant patients with ALL (n=651). In the study, 3 risk groups were defined: low risk (KMT2A germline; n=167); high risk (KMT2A-rearranged and >6 months with WBC count ≥300x10^9/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. The 6-year probability of DFS was comparable for the randomized arms (ADE+MAE 39.3% vs IB 36.8%; log-rank \( P= .47 \)).

**COG AALL0631**

Based on data showing aberrant activation of FLT3 pathway in infant ALL with KMT2A rearrangements, 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. Initial induction consisted of 3 weeks of therapy based on a COG P9407 backbone (cohort 1). 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. 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). 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%]; \( P=.0012 \)). The addition of lestaurtinib did not demonstrate a benefit in outcomes.

**Hematopoietic Stem Cell Transplant**

The benefit derived from using HSCT in infant leukemia is unclear. Several retrospective studies suggest no clinical advantage or a benefit at low EFS rates. 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.

**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. 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 may undergo 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 ≥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; 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. 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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The NCCN Guidelines Staff have no conflicts to disclose.