Acute Lymphoblastic Leukemia, Version 2.2021

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The NCCN Guidelines for Acute Lymphoblastic Leukemia (ALL) focus on the classification of ALL subtypes based on immunophenotype and cytogenetic/molecular markers; risk assessment and stratification for risk-adapted therapy; treatment strategies for Philadelphia chromosome (Ph)-positive and Ph-negative ALL for both adolescent and young adult and adult patients; and supportive care considerations. Given the complexity of ALL treatment regimens and the required supportive care measures, the NCCN ALL Panel recommends that patients be treated at a specialized cancer center with expertise in the management of ALL. This portion of the Guidelines focuses on the management of Ph-positive and Ph-negative ALL in adolescents and young adults, and management in relapsed settings.


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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
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All recommendations are category 2A unless otherwise noted.

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

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

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The complete NCCN Guidelines for 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 Acute Lymphoblastic Leukemia Panel members can be found on page 1109 (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 lymphoma (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 1.8 per 100,000 individuals per year, with approximately 5,690 new cases and 1,580 deaths estimated in 2021. The median age at diagnosis for ALL is 17 years with 53.5% of patients diagnosed at younger than 20 years of age. In contrast, 29.6% of cases are diagnosed at 45 years or older and only approximately 13.7% of patients are diagnosed at 65 years or older. ALL represents 75%–80% of acute leukemias among children, making it the most common form of childhood leukemia; by contrast, ALL represents approximately 20% of all leukemias among adults.

Risk factors for developing ALL include older age (>70 years), exposure to chemotherapy or radiation therapy, and genetic disorders, particularly Down syndrome. Although rare, other genetic conditions have been categorized as a risk factor for ALL and include Li–Fraumeni syndrome, neurofibromatosis, Klinefelter syndrome, Fanconi anemia, Shwachman-Diamond syndrome, Bloom syndrome, and ataxia telangiectasia.

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The cure rates and survival outcomes for patients with ALL have improved dramatically over the past several decades, primarily among children. Improvements are largely owed to advances in the understanding of the molecular genetics and pathogenesis of the disease, the incorporation of measurable residual disease (MRD) testing, the refinement of risk-adapted treatment algorithms, the advent of new targeted agents, and the use of alloge- neic hematopoietic stem cell transplantation (HCT).

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. Improvements are largely owed to advances in the understanding of the molecular genetics and pathogenesis of the disease, the incorporation of measurable residual disease (MRD) testing, the refinement of risk-adapted treatment algorithms, the advent of new targeted agents, and the use of allogeneic hematopoietic stem cell transplantation (HCT).

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30 years. The 5-year OS in this population is 55.8%. Cure rates for AYAs with ALL remain suboptimal compared with those for children, although substantial improvements have been seen with the adoption of pediatric treatment regimens. 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. Favorable cytogenetic subtypes, such as ETV6-RUNXI ALL and hyperdiploidy, occur less frequently among AYA patients compared with children, whereas the incidence of ALL in high-risk subgroups such as BCR-ABL (Ph-positive ALL) or with Ph-like ALL is higher in AYA patients.

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). Laboratory studies include a complete blood count (CBC) with platelets and differential, a blood chemistry profile, liver function tests, a disseminated intravascular coagulation panel (including measurements for D-dimer, fibrinogen, prothrombin time, and partial thromboplastin time), and a tumor lysis syndrome panel (including measurements for serum lactate dehydrogenase, uric acid, potassium, phosphate and calcium). Other recommended tests include hepatitis B/C, HIV, and cytomegalovirus antibody evaluations. Female patients should undergo pregnancy testing and all male patients should be evaluated for testicular involvement of disease, including a scrotal ultrasound; testicular involvement is especially common in cases of T-ALL. Fertility counseling and preservation options should be presented to all patients. CT scans of the neck, chest, abdomen, and pelvis with intravenous contrast are recommended as indicated by symptoms, and if any extramedullary involvement is suspected, a PET/CT may be considered for diagnosis and follow-up.

All patients should be evaluated for opportunistic infections as appropriate. In addition, an echocardiogram or multigated acquisition scan should be obtained 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, and for elderly patients. An early transplant evaluation and donor search should be strongly considered.
Appropriate imaging studies (eg, CT/MRI scan of the head with contrast) should be performed to detect meningeal disease, chloromas, or central nervous system (CNS) bleeding for patients with major neurologic signs or symptoms at diagnosis. CNS involvement should be evaluated through lumbar puncture at timing that is consistent with the treatment protocol. Pediatric-inspired regimens typically include lumbar puncture at diagnostic workup; the NCCN ALL Panel recommends that the first lumbar puncture be performed at the time of initial scheduled intrathecal therapy unless directed by symptoms to perform earlier.

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 subtype, presence of CNS disease, and response to induction/consolidation therapy have been identified as important factors in defining risk and assessing prognosis for both adult and childhood ALL.

Prognostic Factors in AYA Patients With ALL

In 1993, a common set of risk criteria was established by the Pediatric Oncology Group (POG) and Children’s Cancer Group (CCG) at an international conference hosted by the NCI.27 In this system, two risk groups were designated: standard risk and high risk. Standard risk was assigned to patients age 1 to younger than 10 years of age and with a WBC count less than 50,000/µL, whereas all other patients with ALL, including T-ALL (regardless of age or WBC count), were considered high risk.28 It should be noted that despite exclusion from this report, patients younger than age 1 should also be considered very high risk.29,30 The POG and CCG have since merged to form the Children’s Oncology Group (COG) and subsequent risk assessment has produced additional risk factors, particularly in precursor B-ALL, to further refine therapy. Specifically, in B-ALL, a group identified as very high risk, was defined as patients with any of the following characteristics: t(9;22) chromosomal translocation...
(ie, Ph-positive ALL) and/or presence of BCR-ABL1 fusion protein; hypodiploidy (<44 chromosomes); BCR-ABL1–like or Ph-like ALL; iAMP21; or failure to achieve remission with induction therapy. KMT2A rearrangements and a poor response to induction chemotherapy also recategorized patients into this group. Conversely, criteria were refined for lower risk and included patients with hyperdiploidy, the t(12;21) chromosomal translocation (ETV6-RUNX1 subtype), or simultaneous trisomies of chromosomes 4, 10, and 17. Presence of extramedullary disease and the early response to treatment also modified risk. Early marrow response to therapy was a strong positive prognostic factor while the presence of extramedullary disease at diagnosis was correlated with a poorer prognosis. Using the refined risk assessment, four risk categories for B-ALL, designated as low risk, standard risk, high risk, and very high risk, were identified encompassing 27%, 32%, 27%, and 4% of cases, respectively.

Risk stratification of T-ALL has been more difficult than in B-ALL. Although T-cell lineage has previously been considered a high-risk feature in ALL, modern treatment protocols have resulted in improved survival outcomes for these patients. The identification of genetic mutations and the use of targeted therapies may change the way T-ALL is treated and ultimately how these patients are assessed for risk.

Historically, the AYA population has been treated on either a pediatric or an adult ALL regimen, depending on referral patterns and the institution. In recent years, several retrospective studies from both the United States and Europe have shown that AYA patients (15–21 years of age) treated on a pediatric protocol have substantially improved event-free survival (EFS) compared with same-aged patients treated on adult ALL regimens. Comparison of adult and pediatric protocols has shown that adults received lower doses of nonmyelosuppressive chemotherapy and less intense intrathecal chemotherapy regimens. Adult protocols also are more likely to include allogeneic HCT compared with pediatric protocols, but the benefits of HCT in the AYA population have not been sufficiently studied, and the available data include conflicting findings. There is clearly a significant difference between the way adults and pediatric patients are treated and this may be a variable in the treatment of AYA patients. Thus, the choice of initial treatment regimen can have a profound impact on overall clinical outcomes in AYA patients.
Despite improved outcomes for AYA patients treated on pediatric-inspired regimens versus adult ALL regimens, studies have shown poorer outcomes among patients in the AYA group compared with children younger than 10 years. This may be attributed to factors that are based on biology and social differences. Compared with the pediatric population, AYA patients have a lower frequency of favorable chromosomal/cytogenetic abnormalities, such as hyperdiploidy or ETV6-RUNXI, and a greater incidence of poor-risk cytogenetics including Ph-positive ALL, Ph-like ALL, hypodiploidy, and complex karyotype, and a higher incidence of ETP-ALL.

Furthermore, the positive prognostic values of the ETV6-RUNXI mutation and hyperdiploidy are greater in the patients younger than 10 years, suggesting that the benefits decline with age. The effects of treatment are also shown to be different in the AYA population compared with the pediatric population. In vitro studies showed that ALL cells from children older than 10 years are more resistant to chemotherapy compared with the cells from children younger than 10 years. The ALL Panel considers AYA to be within the age range of 15–39 years. However, this age is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages.

Chronological age is a poor surrogate for fitness for therapy. Patients should be evaluated on an individual basis, including for the following factors: end-organ reserve, end-organ dysfunction, and performance status.

For additional considerations in the management of AYA patients with ALL, see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.

Both age and initial WBC count have historically been considered clinically significant prognostic factors in the management of adult patients with ALL. Early prospective multicenter studies defined values for older age (>35 years) and higher initial WBC count (>30 x 10⁹/L for B-cell lineage; >100 x 10⁹/L for T-cell lineage) that were predictive of significantly decreased
remission duration. Subsequent studies have confirmed the prognostic importance of these clinical parameters, although the cutoff values differed between studies.

In one of the largest studies to date (n = 1521), conducted by the Medical Research Council (MRC) UKALL/ECOG, both age (>35 years) and WBC count (>30 × 10⁹/L for B-cell lineage; >100 × 10⁹/L for T-cell lineage) were found to be significant independent prognostic factors for decreased disease-free survival (DFS) and OS among patients with Ph-negative ALL; the independent prognostic value remained significant when these factors were evaluated as continuous variables in multivariate analysis. All patients, regardless of Ph status, had received induction therapy followed by intensification (for patients with a complete response [CR] postinduction) with contemporary chemotherapy combination regimens. Patients with a CR after induction received allogeneic HCT (for patients <50 years of age and with HLA-compatible siblings), autologous HCT, or consolidation/maintenance treatment. Because Ph-positive ALL is associated with a very poor prognosis, patients with this subtype were assigned to undergo allogeneic HCT (including matched, unrelated donor [URD] HCT) when possible. The 5-year OS rate among patients with Ph-positive and Ph-negative disease was 25% and 41%, respectively. Among patients with Ph-negative ALL, those older than 35 years or with elevated WBC count (>30 × 10⁹/L for B-cell lineage; >100 × 10⁹/L for T-cell lineage) at diagnosis were initially identified as high risk, whereas all others were classified as standard risk. The 5-year OS rates for the Ph-negative high-risk and standard-risk subgroups were 29% and 54%, respectively. Further analysis of the Ph-negative population according to risk factors showed that patients could be categorized as low risk (no risk factors based on age or WBC count), intermediate risk (either age >35 years or elevated WBC count), or high risk (both age >35 years and elevated WBC count). The 5-year OS rates based on these risk categories were 55%, 34%, and 5%, respectively, suggesting that patients with Ph-negative ALL in the high-risk subgroup had even poorer survival outcomes than patients in the overall Ph-positive subgroup.

In a subsequent analysis from this MRC UKALL XII/ECOG E2993 study, cytogenetic data were evaluated in approximately 1,000 patients. The analysis confirmed the negative prognostic impact of Ph-positive status compared with Ph-negative disease, with a significantly
**FOOTNOTES**

h See Cytogenetic Risk Groups for B-ALL (ALL-A).

i High WBC count (>30 x 10^9/L for B lineage or >100 x 10^9/L for T lineage) is considered a high-risk factor based on some studies in ALL. Data demonstrating the effect of WBC counts on prognosis are less firmly established for adults than for the pediatric population and likely superseded by MRD quantification after treatment.

j The ALL Panel considers AYA to be within the age range of 15–39 years. However, this age is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages.

k Chronic age is a poor surrogate for fitness for therapy. Patients should be evaluated on an individual basis, including for the following factors: end-organ reserve, end-organ dysfunction, and performance status.

l For additional considerations in the management of AYA patients with ALL, see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.

m All ALL treatment regimens include CNS prophylaxis. See Evaluation and Treatment of Extramedullary Involvement (ALL-B).

n The importance of cytogenetics as a prognostic factor for survival outcomes was shown in other studies, including the SWOG study conducted with 200 adult patients with ALL. More than 50% of patients with low hypodiploidy/near triploidy had substantially decreased 5-year EFS rate (16% vs 36%; P<.001, adjusted for age, gender, and WBC count) and OS rate (22% vs 41%; P<.001, adjusted for age, gender, and WBC count). Among patients with Ph-negative disease, the following cytogenetic subgroups had significantly decreased 5-year EFS (13%–24%) and OS rates (13%–28%) based on univariate analysis: t(4;11) KMT2A translocation, t(8;14), complex karyotype (≥5 chromosomal abnormalities), and low hypodiploidy (30–39 chromosomes)/near triploidy (60–78 chromosomes). In contrast, del(9p) or high hyperdiploidy (51–65 chromosomes) was associated with more favorable 5-year EFS (49%–50%) and OS rates (53%–58%). An earlier report of data from patients treated on the French ALL study group (LALA) protocols suggested that near triploidy (60–78 chromosomes) may be derived from duplication of hypodiploidy (30–39 chromosomes); both aneuploidies were associated with poor DFS and OS outcomes similar to that of patients with Ph-positive ALL.

Based on multivariate Cox regression analysis reported in the MRC UKALL XII/ECOG E2993 study, t(8;14), low hypodiploidy/near triploidy, and complex karyotype remained significant independent predictors for risk of relapse or death; the prognostic impact of these cytogenetic markers was independent of factors such as age, WBC count, or T-cell immunophenotype, and their significance was retained even after excluding patients who had undergone postinduction HCT.

The importance of cytogenetics as a prognostic factor for survival outcomes was shown in other studies, including the SWOG study conducted with 200 adult patients with ALL. In this study, the prognostic impact of the different cytogenetic categories outweighed that of the more traditional factors, such as age and WBC count; in multivariate analysis for both relapse-free survival (RFS) and OS, cytogenetics remained a significant independent predictor of outcomes, whereas factors such as age and WBC count lost prognostic significance. Moreover, the subgroup (n=91) of patients with “very high risk” cytogenetic features [identified based on outcomes from the MRC/ECOG study mentioned earlier: presence of t(4;11) KMT2A (MLL) translocation; t(8;14); complex karyotype; or low hypodiploidy] had substantially decreased 5-year RFS and OS rates (22%, for both endpoints). Analysis by ploidy status was not possible because only 2 patients were considered to have low hypodiploidy/near triploidy. The 5-year RFS and OS rates among patients with Ph-positive ALL (n=36) were 0% and 8%, respectively.
Management of Ph-Positive ALL

Initial Treatment in AYA Patients With Ph-Positive ALL

Ph-Positive ALL is rare in children with ALL, occurring in only approximately 3% of pediatric cases compared with 25% of adult cases. The frequency of Ph-positive ALL among AYA patients ranges from 5% to 25% and increases with age, although this subtype is still uncommon relative to the incidence in older adults. Historically, children and adolescents with Ph-positive disease had a poorer prognosis compared with patients with Ph-negative B-ALL. However, recent improvements in the treatment options are closing this gap.

Hematopoietic Cell Transplant

In a retrospective analysis of children with Ph-positive ALL treated between 1986 and 1996 (n=326) with intensive chemotherapy regimens with or without allogeneic HCT, the 7-year EFS and OS rates were 25% and 36%, respectively. This benefit with HCT versus chemotherapy alone was not observed with autologous HCT or with HCT from matched URDs. This study showed that allogeneic HCT from a matched related donor offered improvements in outcomes over chemotherapy alone.

In a subsequent analysis of outcomes in children with Ph-positive ALL treated between 1995 and 2005 but also without targeted tyrosine kinase inhibitors (TKIs), the 7-year EFS and OS rates were 32% and 45%, respectively. Outcomes with allogeneic HCT from either matched related donors or URDs appeared similar, and HCT improved disease control over intensive chemotherapy alone. Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy. Consider retesting for MRD at first available opportunity.

In a multicenter COG study (AALL-0031) of children and adolescents with high-risk ALL, the group of patients with Ph-positive ALL (n=92; aged 1–21 years) was 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 HCT from a related donor (57%; n = 21) or 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 COG trial (AALL-0622) 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 AALL-0031. The 5-year OS and EFS rates (± standard deviation) were 86% ± 5% and 60% ± 7%, respectively, and outcomes were similar to those observed in AALL-0031.

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 Berlin-Frankfurt-Münster (BFM) backbone intensive treatment versus chemotherapy alone. The study enrolled 108 patients with good risk and 70 patients with poor risk aged 1 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 patients with good risk 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 HCT at first CR (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%).

**Blinatumomab**

Treatment of newly diagnosed Ph-positive ALL adults was evaluated in a phase 2 single-group trial using dasatinib chemotherapy-free induction followed by first-line consolidation therapy blinatumomab. Sixty-three patients, aged 24 to 84 were enrolled. At the end of induction, 29% patients had a molecular response, which increased to 60% after 2 cycles of blinatumomab. ABL1 mutations occurred in 6 patients who had an increase in MRD, however were cleared on treatment with blinatumomab. Few toxic effects of grade 3 or higher were observed, with cytomegalovirus reactivation or infection occurring in 6 patients. As a result of high molecular response, overall and disease-free survival at a median follow-up of 18 months was achieved in 95% and 88% (95% CI, 90–100; 80–97) of patients, respectively. Dis ease-free survival was lower in patients with IKZF1 deletions.

The safety and efficacy of blinatumomab in combination with TKIs has recently been evaluated in the treatment of Ph-positive ALL. In a small retrospective study, adults with relapsed/refractory (R/R) Ph+ ALL (n=9) and chronic myeloid leukemia (CML) (n=3) for whom one line of chemotherapy and one class of TKIs had previously failed, were treated with the combination of blinatumomab and a TKI (ponatinib, dasatinib, or bosutinib). Of the 12 total patients, 75% (9/12) experienced complete molecular responses with no cardiovascular adverse events.
ponatinib in 28 patients with newly diagnosed or relapsed/refractory Ph-positive ALL showed an overall 95% response rate combined.78 In the newly diagnosed cohort, a 1-year EFS and OS of 100% was reported, with no patients undergoing transplant. The 1-year EFS was 55% in the R/R cohort, with 88% OS reported.78 Four patients (44%) with R/R disease underwent HSCT.

**TKIs Combined With Hyper-CVAD**

A phase II study at MD Anderson Cancer Center (MDACC) evaluated imatinib combined with the hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) regimen in patients with previously untreated Ph+ ALL (n=54; median age, 51 years; range, 17–84 years); 14 patients underwent subsequent allogeneic HCT.79 The 3-year OS rate with this regimen was 54%. Among the patients aged 40 years or younger (n=16), a strong trend was observed for OS benefit with allogeneic HCT (3-year OS rate, 90% vs 33%; P=.05).79 Among patients aged 60 years or younger, no statistically significant difference was observed in the 3-year OS rate between patients who received HCT and those who did not (77% vs 57%).

Studies have shown the promising activity of other TKIs, including dasatinib and ponatinib when incorporated into frontline regimens for patients with ALL. In a phase II study from MDACC, dasatinib was combined with hyper-CVAD and subsequent maintenance therapy in patients with previously untreated Ph-positive ALL (n=35; median age, 53 years; range, 21–79 years; 31% were older than 60 years); 4 of the patients received allogeneic HCT in CR1.80 The 2-year OS and EFS rates were 64% and 57%, respectively. The efficacy and safety of ponatinib combined with hyper-CVAD was examined in patients with Ph-positive ALL (n=37; aged ≥18 years; median age, 51 years; 12 patients were ≥60 years) in a phase II prospective trial.81 Of the 32 patients with Ph-positive metaphases at the start of therapy, an overall complete cytogenetic response was observed in 32 patients (100%). By multiparametric flow cytometry, 35 of 37 patients (95%) had no MRD after a median of 3 weeks of therapy.81 However, it is worth noting that only half of the patients 60 years or older were able to complete therapy with this regimen and were switched to alternate TKIs. The 2-year OS and EFS rates were 80% and 81%, respectively. A follow-up study (n=76; age ≥18 years; median age, 47 years) demonstrated long-term efficacy for ponatinib and hyper-CVAD with a 3-year EFS rate of 70%.82

**TKIs Combined With Multiagent Chemotherapy**

In the phase II study from the Group for Research on Adult ALL (GRAALL; GRAAPH-2003), patients with previously untreated Ph-positive ALL (n=45; median age, 45 years; range, 16–59 years) received imatinib in combination with chemotherapy during either induction or consolidation therapy.83,84 Patients in complete remission with a donor received allogeneic HCT (n=24), whereas those in complete remission with good molecular response but without a donor were eligible for autologous HCT (n=10). Nine patients did not receive HCT and were treated with imatinib-based maintenance therapy. The 4-year OS rate did not differ significantly for patients with a sibling donor compared with patients undergoing autologous HCT (76% vs 80%). The 4-year OS for patients who received only maintenance imatinib was 33%.84 These data suggest that improved survival with imatinib-based therapy can be further enhanced by the addition of HCT.

In the subgroup of patients with Ph-positive ALL (n=94; median age, 47 years; range, 19–66 years) from the Northern Italy Leukemia Group study (NILG-09/00), outcomes were compared among patients who received chemotherapy with imatinib (n=59) or without imatinib (n=35), with or without subsequent HCT (allologous or autologous).85 The patients who received imatinib (63% of eligible patients underwent allogeneic HCT) had significantly higher 5-year OS (38% vs 23%; P=.009) and DFS rates (39% vs 25%; P=.044) compared with those who did not receive imatinib (39% of eligible patients underwent allogeneic HCT).85 The 5-year OS rates by treatment type were 47% for allogeneic HCT (n=45), 67% for autologous HCT (n=9), 30% for imatinib without HCT (n=15), and 7% for no imatinib and no HCT (n=13); the corresponding treatment-related mortality rates were 17%, 0%, 36%, and 23%, respectively. The 5-year relapse rates were 43%, 33%, 87%, and 100%, respectively.85

The Japan Adult Leukemia Study Group (ALL-202) treated patients with Ph-positive ALL (n=100) with chemotherapy combined with imatinib administered during induction, consolidation, and maintenance phases.86,87 An early analysis (n=80; median age, 48 years; range, 15–63 years) reported a 1-year OS rate of 73% among patients who underwent allogeneic HCT, compared with 85% for those who did not.87 A subsequent analysis compared outcomes for the subgroup of patients who received allogeneic HCT at first CR in this study (n=51; median age, 38 years; range, 15–64 years) versus those for a historical cohort of patients who received allogeneic HCT without prior imatinib (n=122).86 The 3-year OS (65% vs 44%; P=.015) and DFS rates (58% vs 37%; P=.039) were significantly higher among patients treated with imatinib compared with the historical cohort; the 3-year nonrelapse mortality rate was similar between cohorts (21% vs 28%, respectively).86

A multicenter phase II study from the Adult Acute Lymphoblastic Leukemia Working Party of the Korean
Society of Hematology investigated the effects of multiagent chemotherapy combined with nilotinib in patients with newly diagnosed Ph-positive ALL (n=90; median age, 47 years; range, 17–71 years). Chemotherapy combined with nilotinib was administered during induction, consolidation, and maintenance phases. Of 90 evaluable patients, 82 (91%) experienced complete hematologic remission with a median time of 27 days (range, 13–72). The 2-year hematologic RFS and OS rates were both 72%. In a phase II multicenter trial (CALGB 10701), patients with newly diagnosed Ph-positive ALL (n=64; median age, 60 years; range, 22–87 years) were treated with multiagent chemotherapy combined with dasatinib, and the efficacy of different postremission strategies were evaluated including allogeneic HCT, autologous HCT, and chemotherapy alone, followed by maintenance with dasatinib. The CR rate was 97% with no induction deaths. With a median follow-up of 46 months for survivors, 3-year OS and DFS were 55% and 43%, respectively. For patients who underwent consolidation with allogeneic HCT, autologous HCT, or chemotherapy, 3-year OS was 75%, 71%, and 55%, respectively, with median OS not reached for all groups. The 3-year DFS was 55%, 43%, and 46%, respectively.

### Treatment of Relapsed Ph-Positive ALL

The treatment of patients who experience relapse after initial therapy for ALL remains a challenge, because these patients have a very poor prognosis. Several large studies using conventional chemotherapy for relapsed adult patients have reported a median OS of 4.5 to 6 months, and a 5-year OS rate of 3%–10%. One major factor associated with poorer survival outcomes after subsequent therapy for relapsed ALL is the duration of response to frontline treatment. In an analysis of data from the PETHEMA (Programa Español de Tratamientos en Hematología) trials, patients with disease that relapsed more than 2 years after frontline therapy had significantly higher 5-year OS rates than the groups of patients who relapsed within 1 to 2 years or within 1 year of frontline therapy (31% vs 15% vs 2%; \( P<.001 \)). Similarly, in the MRC UKALL XII/ECOG E2993 trial, patients with disease that relapsed more than 2 years after initial diagnosis and frontline therapy had a significantly higher 5-year OS rate than those who relapsed within 2 years (11% vs 5%; \( P<.001 \)). In the pre-imatinib era, patients with Ph-positive ALL who relapsed after frontline therapy had dismal outcomes; subgroup data from the large, prospective trials LALA-94 and MRC UK XII/ECOG E2993 showed a median OS of 5 months and a 5-year OS rate of 3%–6% among patients subsequently treated for relapsed Ph-positive ALL.

### Hematopoietic Cell Transplant

Treatment options are extremely limited for patients with Ph-positive ALL who experience relapse after receiving consolidation with allogeneic HCT. Some investigators have reported on the feasibility of inducing a second molecular CR with dasatinib in those who have experienced an early relapse after first allogeneic HCT, which allowed for a second allogeneic HCT. Studies that include donor lymphocyte infusion (DLI) to induce further graft-versus-leukemia effect in those who relapse after allogeneic HCT have reported little to no benefit, though it has been suggested that this is due to excessively high leukemic burden. Indeed, published case reports have suggested that the use of DLI for residual disease or molecular relapse (as noted by levels of BCR-ABL fusion mRNA measured with PCR) after allogeneic HCT may eliminate residual leukemic clones and thereby prevent overt hematologic relapse. Moreover, case reports have described using newer TKIs, such as dasatinib and nilotinib, along with DLI to manage relapse after allogeneic HCT. Although these approaches are promising, only limited data are available. Evidence from prospective studies is needed to establish the role of DLI, with or without TKIs, in the treatment of relapsed disease.

### Tyrosine Kinase Inhibitors

The emergence of resistance poses a challenge for patients relapsing after initial treatment with TKI-containing regimens. Point mutations within the ABL kinase domain and alternative signaling pathways mediated by the SRC family kinase have been implicated as mechanisms of resistance. The former has been identified in a large proportion of patients who experience disease recurrence after imatinib-containing therapy. Moreover, ABL kinase domain mutations may be present in a small group of imatinib-naïve patients even before initiation of any TKI therapy. CNS relapse has been reported in both patients with disease responsive to imatinib therapy (isolated CNS relapse with CR in marrow) and patients with disease resistant to imatinib therapy. The concentration of imatinib in the cerebrospinal fluid has been shown to be approximately 2 logs lower than that achieved in the blood, suggesting that this agent does not adequately penetrate the blood-brain barrier to ensure CNS coverage. A study showed that among patients with ALL treated with imatinib and who did not receive routine prophylactic intrathecal therapy or cranial irradiation, 12% developed CNS leukemia. Patients with imatinib-resistant disease who developed CNS disease rapidly died of progressive disease; conversely, patients with imatinib-sensitive disease who developed isolated CNS
relapse could be successfully treated with intrathecal therapy with or without cranial irradiation.110,112

Dasatinib and nilotinib are second-generation TKIs that have shown greater potency in inhibiting BCR-ABL compared with imatinib, and retention of antileukemic activity in cells with certain imatinib-resistant ABL mutations.114–117 In addition, dasatinib has better CNS penetration than imatinib, and therefore may have advantages in preventing CNS relapse. Both TKIs have been evaluated as single-agent therapy in patients with Ph-positive ALL that is resistant to imatinib treatment.118–120 A randomized phase III study examined the activity of dasatinib administered as once-daily (140 mg daily) versus twice-daily (70 mg twice daily) dosing in patients with Ph-positive leukemia resistant to imatinib119, the once-daily dosing resulted in a higher response rate (major cytogenetic response) than the twice-daily dosing (70% vs 52%). Although the median OS was shorter with the once-daily dosing (6.5 vs 9 months), the median progression-free survival was longer (4 vs 3 months).119 These differences in outcomes between the dosing arms were not statistically significant.

Dasatinib in combination with the hyper-CVAD regimen (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) was investigated in a phase II trial that included patients with Ph-positive relapsed ALL (n = 19) and lymphoid blast phase (BP) CML (n = 15).121 An overall response rate (ORR) of 91% was obtained with 26 patients (84%) experiencing complete cytogenetic remission, 13 patients (42%) having complete molecular response, and 11 patients (35%) having a major molecular response. There were 9 patients who went on to receive allogeneic HCT, including 2 patients with ALL. In the patients with relapsed ALL, 30% remained in complete remission at 3 years with a 3-year OS of 26%. At the median follow-up of 52 months (range, 45–59 months), 2 patients (11%) with ALL were still alive.

Bosutinib, a second-generation TKI that acts as a dual inhibitor of BCR-ABL and SRC family kinases,122–123 was approved in September 2012 by the FDA for the treatment of chronic, accelerated phase, or BP Ph-positive CML in adult patients with resistance to prior TKI treatment based on an open-label, multicenter phase I/II trial.123 Efficacy and safety analyses of bosutinib monotherapy included patients with advanced leukemia [accelerated phase CML (n = 79), BP CML (n = 64), or ALL (n = 24)] who were previously treated with at least one TKI.124,125 Of the 22 evaluable patients with ALL, 2 patients (9%) attained or maintained a confirmed overall hematologic response by 4 years.124 Common overall treatment-related adverse events reported in patients with advanced leukemia included diarrhea (74%), nausea (48%), and vomiting (44%).124,125

Ponatinib is a third-generation TKI that was initially approved by the FDA in December 2012 for the treatment of adult patients with chronic, AP, or BP Ph-positive CML or Ph-positive ALL, with resistance to prior therapy, and was added as a treatment option for R/R Ph-positive ALL in 2013. Though temporarily removed from the market in November 2013, ponatinib distribution resumed in December 2013 following revision to both the prescribing information and risk evaluation and mitigation strategies program to address the risk for serious cardiovascular adverse events. This TKI has been shown to inhibit both native and mutant forms of BCR-ABL (including those resulting from T315I mutation) in preclinical studies.126 In a multicenter, open-label, phase II study (PACE trial; n = 449), ponatinib showed substantial activity in patients with Ph-positive leukemias resistant or intolerant to second-generation TKIs.127 Major hematologic response was observed in 41% of the subgroup with Ph-positive ALL (n = 32). In the subset of patients with Ph-positive ALL with ABL T315I mutation (n = 22), major hematologic response was observed in 36%.127 Common overall treatment-related adverse events in the PACE trial included thrombocytopenia (37%), rash (34%), and dry skin (32%). Additionally, arterial thrombotic events were observed and 7.1% of patients experienced cardiovascular events,127 though dose reduction may impart a lower risk.

Not all imatinib-resistant ABL mutations are susceptible to the newer TKIs. For instance, dasatinib is not as active against cells harboring the ABL mutations T315I, V299L, and F317L.105–115,128–129 Thus, for patients with disease resistant to TKI therapy, it becomes important to identify potential ABL mutations that may underlie the observed resistance to treatment. A panel of experts from the European LeukemiaNet published recommendations for the analysis of ABL kinase domain mutations in patients with CML, and treatment options according to the presence of different ABL mutations.130

**Blinatumomab**

In December 2014, the FDA approved blinatumomab for the treatment of relapsed or refractory Ph-negative precursor B-AL. In July 2017, blinatumomab received full approval from the FDA for the treatment of R/R precursor B-ALL (Ph-negative and Ph-positive). A follow-up, open-label, single-arm, multicenter, phase II study evaluated the efficacy and safety of blinatumomab in patients with R/R Ph-positive ALL who had progressed after imatinib and at least one second- or third-generation TKI (n = 45).131 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.131 Notably, responses were independent of T315I mutation status.
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 leukemia. The overall incidence of severe adverse events was similar across treatment arms, with a higher incidence of hepatic veno-occlusive disease observed in the inotuzumab group, related in part to dual alkylator-based transplant conditioning administered in remission. These data translated into a significant benefit in the median duration of remission (4.6 vs 3.1 months; P=.03), median progression-free survival (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 R/R precursor B-ALL.

CAR T Cells

Currently, bone marrow transplant is the only cure for R/R ALL, but many patients are not eligible for transplant based on age or progression of the disease. The generation of CAR T cells to treat ALL represents a significant advance in the field and has shown significantly greater OS than current regimens. The pretreatment of patients with CAR T cells has served as a bridge for transplant, and patients who were formerly unable to be transplanted due to poor remission status achieve a CR and ultimately proceed to transplantation. CAR T-cell therapy relies on the genetic manipulation of a patients’ T cells to engender a response against a leukemic cell-surface antigen, most commonly CD19 (see “Treatment of Relapsed Ph-Negative ALL” [page 1098] for a detailed discussion of CAR T cells). CAR T-cell therapy/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-ALL.

Management of Ph-Negative ALL

Initial Treatment in AYA Patients With Ph-Negative ALL

The AYA population with ALL can pose a unique challenge given that patients may be treated with either a pediatric or an adult protocol, depending on local referral patterns and institutional practices. Retrospective analyses based on cooperative group studies from both the United States and Europe have consistently shown the superior outcomes for AYA patients (aged 15–21 years) treated on pediatric versus adult ALL regimens. In the AYA population, 5-year EFS rates ranged from 63% to 74% for patients treated on a pediatric study protocol versus 34%–49% for those receiving the adult protocol. In a retrospective comparative study that analyzed outcomes of AYA patients (aged 16–20 years) treated on a pediatric CCG study protocol (n=197; median age, 16 years) versus an adult CALGB study protocol (n=124; median age, 19 years), patients treated on the pediatric regimen compared with those on the adult regimen had significantly improved 7-year EFS (63% vs 34%, respectively; P<.001) and OS (67% vs 46%, respectively; P<.001) rates. Moreover, AYA patients treated on the adult protocol experienced a significantly higher rate of isolated CNS relapse at 7 years (11% vs 1%; P=.006). The substantial improvements in outcomes observed with the pediatric regimen during this study, and in the earlier retrospective analyses from other cooperative groups, may be largely attributed to the use of greater cumulative doses of drugs, such as corticosteroids (prednisone and/or dexamethasone), vincristine, and l-asparaginase, and to earlier, more frequent, and/or more intensive CNS-directed therapy compared with adult regimens. Given the success seen with multiagent intensive chemotherapy regimens for pediatric patients with ALL, several clinical trials have evaluated pediatric-inspired regimens for the AYA patient population.

Hematopoietic Cell Transplant

For AYA patients with Ph-negative ALL in first CR, allogeneic HCT may be considered for high-risk cases—particularly for patients with disease that is MRD positive any time after induction; or patients with elevated WBC counts; or patients with B-ALL and poor-risk cytogenetics (eg, hypodiploidy, KMT2A (MLL) rearrangement) at diagnosis. A large multicenter trial (LALA-94 study) evaluated the role of postinduction HCT as one of the study objectives in adolescent and adult ALL patients receiving therapy for previously untreated ALL (n=922; median age, 33 years; range, 15–55 years). Patients were stratified into 4 risk groups: (1) Ph-negative standard-risk disease (defined as achievement of CR after 1 course of chemotherapy; absence of CNS disease; absence of t(4;11), t(1;19), or other 11q23 rearrangements; WBC count <30 × 10^9/L); (2) Ph-negative high-risk ALL (defined as patients with non-standard-risk disease and without CNS involvement); (3) Ph-positive ALL; and (4) evidence of CNS disease. After induction therapy, patients with Ph-negative high-risk ALL were eligible to undergo allogeneic HCT if a matched sibling donor was available;
those without a sibling donor were randomized to undergo autologous HCT or chemotherapy alone. Among the subgroup of patients with Ph-negative high-risk ALL (n=211), the 5-year DFS and OS rates were 30% (median, 16 months) and 38% (median, 29 months), respectively. Based on intent-to-treat analysis, outcomes in patients with Ph-negative high-risk ALL were similar for autologous HCT (n=70) and chemotherapy alone (n=59) in terms of median DFS (15 vs 11 months), median OS (28 vs 26 months), and 5-year OS rate (32% vs 21%). Outcomes were improved in patients with Ph-negative high-risk ALL and those with CNS involvement allocated to allogeneic HCT. The median DFS was 21 months for these patients, and the median OS has not yet been reached; the 5-year OS rate was 51%. Thus, it appears that in patients with Ph-negative high-risk disease, allogeneic HCT in first CR improved DFS outcomes, whereas autologous HCT did not result in significant benefit compared with chemotherapy alone.

In the PETHEMA ALL-93 trial, adult patients with high-risk ALL (defined as having at least one of the following criteria: 30–50 years of age; WBC count ≥25 × 10⁹/L; presence of t(9;22), t(4;11), or other 11q rearrangements; and t(1;19)) received postremission induction therapy (n=222 eligible; median age, 27 years; range, 15–50 years) with allogeneic HCT (n=84; if matched related donor available), autologous HCT (n=50), or chemotherapy alone (n=48). Based on intent-to-treat analysis of data from patients with Ph-negative high-risk disease, no significant advantage was observed in a donor versus no-donor comparison of median DFS (21 months vs 38 months), median OS (32 vs 67 months), 5-year DFS rate (37% vs 46%), or 5-year OS rate (40% vs 49%). In addition, when the analysis was conducted based on the actual postremission treatment strategy for patients who underwent URD HCT during first CR, 60 patients (36%) had one poor prognostic factor and 97 (57%) had none. A donor versus no-donor comparison in all patients with Ph-negative ALL showed that the 5-year OS rate was significantly higher in the donor group than in the no-donor group (53% vs 45%; P=.01). This advantage in OS outcomes for the donor group was observed for patients with standard risk (62% vs 52%; P=.02) but not for those with Ph-negative high-risk disease (41% vs 35%). This was partly because of the high rate of nonrelapse mortality observed with the donor group compared with the no-donor group in patients with high-risk disease (36% vs 14% at 2 years). Among patients with standard risk, the nonrelapse mortality rate at 2 years was 19.5% for the donor group and 7% for the no-donor group. Relapse rate was significantly lower in the donor group than in the no-donor group for both patients with standard risk (24% vs 49%; P<.001) and those with high risk (37% vs 63%; P<.001). Nevertheless, the high nonrelapse mortality rate in the donor group among patients with high-risk disease seemed to diminish the advantage of reduced risk for relapse in this group. This study suggested that allogeneic HCT in first CR was beneficial in patients with standard-risk ALL.

The benefit of matched sibling allogeneic HCT in adult patients with standard-risk ALL was also reported by the HOVON cooperative group. In a donor versus no-donor analysis of patients with standard-risk ALL undergoing postremission therapy with matched sibling allogeneic HCT or autologous HCT, the donor arm was associated with a significantly reduced 5-year relapse rate (24% vs 55%; P<.001) and a higher 5-year DFS rate (60% vs 42%; P=.01) compared with the no-donor arm. In the donor group, the nonrelapse mortality rate at 5 years was 16% and the 5-year OS rate was 69%.

As evidenced by the previously described studies, matched sibling HCT has been established as a valuable treatment strategy for patients with both standard and high-risk Ph-negative ALL, but subsequent studies have examined the role of URD transplants in high-risk Ph-negative ALL. In a retrospective analysis of 169 patients who underwent URD HCT during first CR, 60 patients (36%) had one poor prognostic factor and 97 (57%) had multiple risk factors. The 5-year survival was 39%, which is higher than survival reported in studies of high-risk patients receiving chemotherapy alone. The most significant percentage of treatment-related mortality occurred in patients who were given mismatched donors compared with partially or well-matched donors. There was no significant difference in outcome between older and younger patients, suggesting that URD transplants may be an option for older patients. In a follow-up retrospective study by the same group, RIC was evaluated to lower treatment-related mortality. RIC conditioning most commonly comprised busulfan (9 mg/kg or less), melphalan (150 mg/m²), low-dose total body irradiation (TBI) (less than 500 cGy single dose or less than 800 cGy
fractionated), or fludarabine plus TBI of 200 cGy. RIC is more prominent in the treatment of older patients; therefore, the median age for patients receiving full-intensity (FI) conditioning was 28 years (range, 16–62 years), and for patients receiving RIC, the median age was 45 years (range, 17–66 years). Despite the variation in age, results from the study have shown no difference in relapse (35% vs 26%, \( P=0.08 \)) or in treatment-related mortality (FI, 33%; 95% CI, 31%–36% vs RIC, 32%; 95% CI, 23%–43%; \( P=0.86 \)) at 3 years. \(^{141}\) The 3-year survival for HCT was similar after first CR (FI, 51%; 95% CI, 48%–55% vs RIC, 45%; 95% CI, 31%–59%) and second CR (FI, 33%; 95% CI, 30%–37% vs RIC, 28%; 95% CI, 14%–44%). The DFS was similar in both groups following first CR (FI, 49%; 95% CI, 45%–53% vs RIC, 36%; 95% CI, 23%–51%) and in second CR (FI, 32%; 95% CI, 29%–36% vs RIC, 27%; 95% CI, 14%–43%). \(^{141}\)

A systematic review and meta-analysis of published randomized trials on postremission induction therapy in adults with ALL reported a significant reduction in all-cause mortality with allogeneic HCT in first CR (RR, 0.88; 95% CI, 0.80–0.97) compared with autologous HCT or chemotherapy. \(^{142}\) A subgroup analysis showed a significant survival advantage with allogeneic HCT in standard-risk ALL, whereas a nonsignificant advantage was seen in high-risk ALL. \(^{142}\) Autologous HCT in first remission was not shown to be beneficial relative to chemotherapy in several large studies and meta-analyses. \(^{42,43,142-143}\)

**CCG-1961**

The CCG-1961 trial was a seminal study that allowed comparison of adult versus pediatric regimens in AYA patients. In an analysis of outcomes in children and AYA patients treated in the Dana-Farber Cancer Institute (DFCI) ALL Consortium Protocols (1991–2000), the 5-year EFS rate among younger AYA patients (age 15–18 years; \( n=51 \)) was 78%, which was not significantly different from the EFS rates observed for children aged 10 to 15 years (77%; \( n=108 \)) or those aged 1 to 10 years (85%; \( n=685 \)). \(^{144}\) The CCG 1961 study was designed to evaluate the benefit of augmented versus standard postinduction intensification therapy in children aged 1 to 9 years with high WBC counts (\( \geq 50 \times 10^9/L \)) or in older children and adolescents aged 10 to 21 years. \(^{145}\) Patients were stratified by their initial response to induction therapy as either slow early responders (patients with \( >25\% \) bone marrow blasts on day 7 of induction) or rapid early responders. Among the patients who were rapid early responders to induction (\( n=1,299 \)), the augmented postinduction intensity arm was associated with significantly increased rates of 5-year EFS (81% vs 72%; \( P<0.0001 \)) and OS (89% vs 83%; \( P=0.003 \)) compared with the standard-intensity arm. \(^{145}\) In the subgroup of AYA patients (age 16–21 years; \( n=262 \)) from the CCG 1961 study treated with either augmented or standard-intensity regimens, the 5-year EFS and OS rates were 71.5% and 77.5%, respectively. \(^{146}\) Among the AYA patients who were considered rapid early responders, the augmented-intensity (\( n=88 \)) and standard-intensity (\( n=76 \)) arms showed no statistically significant differences in rates of 5-year EFS (82% vs 67%, respectively) or OS (83% vs 76%, respectively). For the AYA patients who were considered slow early responders (all of whom received the augmented-intensity regimen), the 5-year EFS rate was 71%. \(^{146}\)

**COG AALL0232**

The AALL0232 trial enrolled 2,154 patients between the ages of 1 and 30 years who were diagnosed with high-risk B-ALL. \(^{147}\) In this study, patients were randomly assigned to receive dexamethasone versus prednisone during induction and high-dose methotrexate versus Capizzi escalating-dose methotrexate plus pegaspargase (PEG) during interim maintenance 1. High-dose methotrexate showed improved 5-year EFS (80% vs 75%; \( P=0.008 \)) and OS (88.9% \( \pm \) 1.2% vs 86.1% \( \pm \) 1.4%; \( P=0.25 \)) rates compared with Capizzi escalating-dose methotrexate. 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 60 mg/m²/day of prednisone 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 aged 10 years or older. These data suggest that age may be an important factor for the selection of a corticosteroid. \(^{147}\)

**PETHEMA ALL-96 Regimen**

In the PETHEMA ALL-96 trial, adolescent (\( n=35 \); aged 15–18 years) and young adult (\( n=46 \); aged 19–30 years) patients with standard-risk Ph-negative ALL \( \text{[defined as WBC count <} 30 \times 10^9/L; \text{absence of t(9;22), t(1;19), t(4;11), or any other 11q23 rearrangements]} \) received frontline therapy with a 5-drug induction regimen (vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide), consolidation/reinduction, and maintenance, along with triple intrathecal therapy throughout the treatment period. \(^{148}\) The 6-year EFS and OS rates for the entire patient cohort were 61% and 69%, respectively. No difference in EFS rate was observed between adolescents (60%; 95% CI, 43%–77%) and young adults (63%; 95% CI, 48%–78%); similarly, no significant difference was observed in OS for adolescents (77%; 95% CI, 63%–91%) versus young adults (63%; 95% CI, 46%–80%). \(^{148}\) Based on multivariate regression analysis, slow response to induction therapy (defined as having \( >10\% \) blast cells in the bone marrow aspirate performed on day 14 of treatment) was the only factor associated
with a poor EFS (odds ratio [OR], 2.99; 95% CI, 1.25–7.17) and OS (OR, 3.26; 95% CI, 1.22–8.70).\(^{148}\)

**DFCI ALL Regimen Based on DFCI Protocol 00-01**

A multicenter phase II trial evaluated the pediatric-inspired regimen based on the DFCI Childhood ALL Consortium Protocol 00-01 in AYA and adult patients (aged 18–50 years) with previously untreated ALL; 20% of the patients in this study had Ph-positive disease.\(^{149}\) The treatment regimen comprised induction (vincristine, doxorubicin, prednisone, L-asparaginase, and high-dose methotrexate), triple intrathecal therapy, intensification, and maintenance. Among the 75 patients with evaluable data, the estimated 2-year EFS and OS rates were 72.5% and 77%, respectively.\(^{149}\) Adverse events included 1 death from sepsis (during induction), pancreatitis in 9 patients (12%; including 1 death), osteonecrosis in 2 patients (3%), thrombosis/embolism in 14 patients (19%), and neutropenic infection in 23 patients (31%).\(^{149}\) After a median follow-up of 4.5 years, the 4-year DFS rate for patients with Ph-negative ALL (n=64) and those who achieved CR was 71% (95% CI, 58%–81%), and the 4-year OS rate for all patients with Ph-negative ALL was 70% (95% CI, 58%–79%).\(^{150}\) A phase II successor trial was initiated to determine whether pegylated-asparaginase could be substituted for L-asparaginase in this regimen.\(^{151}\) A high frequency of asparaginase toxicities precipitated reverting to L-asparaginase during induction and a dose-reduction of pegylated-asparaginase during consolidation. After 4 weeks, the CR rate was 89%, and with a median follow-up of 39 months, the estimated 3-year DFS and OS rates were 73% and 75%, respectively.\(^{151}\) These data suggest that intensive pediatric regimens are feasible, with potential modifications, in young adults with previously untreated ALL; however, further follow-up data are needed to evaluate long-term survival outcomes.

**GRAALL-2005 Regimen**

The prospective phase II GRAALL-2003 study evaluated a pediatric-inspired regimen using intensified doses of vincristine, prednisone, and asparaginase for adolescents and adults with Ph-negative ALL (n=225; median age, 31 years; range, 15–60 years).\(^{152}\) The induction regimen comprised vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide. Patients with high-risk disease and donor availability were allowed to proceed to allogeneic HCT. The EFS and OS rates at 42 months were 55% and 60%, respectively. When data from patients who underwent transplantation at first CR were censored, the DFS rates at 42 months were 52% for patients with high-risk disease and 68% for patients with standard-risk disease (risk assignment based on GRAALL protocol); these DFS outcomes by risk groups were similar to outcomes using the MRC UKALL/ECOG definition for risk classification.\(^{152}\) Advanced age was predictive of poorer survival outcomes on this study; the OS rate at 42 months was 41% for patients older than 45 years compared with 66% for those aged 45 years or younger. Moreover, compared with the younger cohort, patients older than 45 years had a higher cumulative incidence of therapy-related deaths (23% vs 5%) and deaths in first CR (22% vs 5%).\(^{152}\) Thus, it seems that the benefit of this pediatric-inspired regimen outweighed the risks for therapy-related deaths only for those patients up to 45 years of age with Ph-negative ALL. The design of the GRAALL-2005 study was similar to the GRAALL-2003 trial, with the addition of randomized evaluation of hyperfractionated cyclophosphamide during induction and late intensification, as well as randomized evaluation of rituximab in patients with CD20-positive Ph-negative ALL (n=209; median age, approximately 40 years; range, 18–59 years).\(^{153}\) The estimated 2-year EFS rate in the rituximab group was 65% (95% CI, 56%–75%) compared with the control group at 52% (95% CI, 43%–63%). After a median follow-up of 30 months, EFS was longer in the rituximab group than in the control group (HR, 0.66; 95% CI, 0.45–0.98; P=.04).\(^{153}\)

**USC/MSKCC ALL Regimen Based on CCG-1882 Regimen**

The USC ALL trial based on the pediatric CCG-1882 regimen has studied the regimen of daunorubicin, vincristine, prednisone, and methotrexate with augmented PEG in patients between the ages of 18 years and 60 years of age with newly diagnosed ALL (n=51).\(^{154,155}\) The augmented arm included one long-lasting PEG dose in each cycle of the 6 total scheduled doses. Each dose of PEG (2000 IU/m² intravenous) was preceded with hydrocortisone for hypersensitivity prophylaxis followed by 1 to 2 weeks of oral steroids. Patients on this trial received a mean of 3.8 doses per patient with 45% of patients receiving all 6 doses, while 20% of patients discontinued treatment based on toxicity. The 7-year OS was 51% (58% of these patients were Ph-negative) and the 7-year DFS was 58%. The dose of PEG was lower than the FDA-approved dose of 2500 IU/m² and adjustments to the dosing interval were made to be greater than or equal to 4 weeks. This deviated from the pediatric protocol to account for the difference in drug enzymatic activity in adults. Study data suggest that adaptation of the pediatric regimen to the adult population may be feasible with modifications to reduce toxicity.

**CALGB 10403 Regimen**

A multicenter phase II Intergroup study (CALGB 10403) was conducted to evaluate a pediatric-inspired regimen in the treatment of AYA patients with Ph-negative ALL. One of the study objectives was to compare the outcomes of patients treated in this trial with those of a
similar group of patients (in regard to age and disease characteristics) treated by pediatric oncologists in the COG trial (AALL-0232). The treatment protocol included a 4-drug induction regimen with intrathecal cytarabine and intrathecal methotrexate, consolidation, interim maintenance, delayed intensification, maintenance (for 2–3 years), and radiotherapy (for patients with testicular or CNS disease or those with T-ALL). Results from 295 evaluable patients (median age, 24 years; range 17–39 years) reported 2 postremission deaths and 3% overall treatment-related mortality. The median EFS was 78.1 months (95% CI, 41.8 months to NR) and the 3-year EFS rate was 59% (95% CI, 54%–65%). The estimated 3-year OS rate was 73% (95% CI, 68%–78%). It was also noted that postinduction MRD-positivity, Ph-like gene expression signatures and obesity were associated with worse treatment outcomes.

**COG AALL0434 Regimen**

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 2 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-ALL who received nelarabine (n = 47) and those who did not (n = 47). No significant differences were observed in the occurrence of neurologic adverse events between these groups, including peripheral motor neuropathy, peripheral 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.

Results from the efficacy phase of this study evaluated data from 1,895 patients with newly diagnosed T-ALL and T-LL. 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-LL all received prophylactic or therapeutic cranial irradiation and were randomized into arms with or without nelarabine (650 mg/m²/day). The 4-year DFS rate for patients with T-ALL in the nelarabine arm (n = 323) versus those who did not receive nelarabine (n = 336) was 88.9% ± 2.2% and 83.3% ± 2.5%, respectively (P = .0332). Compared with the high-dose methotrexate and nelarabine arm, use of escalating-dose methotrexate and nelarabine appeared to enhance the 4-year DFS rates. Another report from the COG AALL0434 study determined that compared with high-dose methotrexate, escalating-dose methotrexate combined with augmented BFM chemotherapy improves DFS and OS outcomes in patients with T-ALL.

A single-arm phase II study from the MDACC evaluated the efficacy of hyper-CVAD plus nelarabine as frontline therapy in adult patients with T-ALL (n = 23). With a median follow-up of 30.4 months (range, 2.4–69.2 months), the CR rate for patients with T-ALL was 89%; however, a trend for inferior DFS and OS was observed for patients with ETP ALL. After a median follow-up of 42.5 months, the 3-year complete remission duration and OS rates were 66% (95% CI, 52%–77%) and 65% (95% CI, 51%–76%), respectively. These studies suggest that for patients with T-ALL, the addition of nelarabine to frontline therapy may be a promising approach.

**Hyper-CVAD With or Without Rituximab**

The hyper-CVAD regimen constitutes another commonly used ALL treatment regimen for adult patients. A phase II study from MDACC evaluated hyper-CVAD in adolescents and adults with previously untreated ALL (n = 288; median age, 40 years; range, 15–92 years; Ph-positive in 17%). The median OS for all patients was 32 months and the 5-year OS rate was 38%, with a median follow-up of 63 months. Among the patients with Ph-negative ALL (n = 234), the 5-year OS rate was 42%. Among patients who experienced a CR (92% of all patients), the 5-year CR duration rate was 38%. Death during induction therapy occurred in 5% of patients, and was more frequent among patients aged 60 years or older. The 5-year OS in patients aged 60 or older was 17%. A subsequent retrospective review from the same institution suggested that this may be related to higher rates of death in remission (34%) relative to younger patients (7%). Based on retrospective analyses of data from adults with B-ALL treated in clinical trials, CD20 positivity (generally defined as CD20 expression on >20% of blasts) was found to be associated with adverse outcomes measured by a higher cumulative incidence of relapse, decreased CR duration, or decreased survival. Given the prognostic significance of CD20 expression in these patients, treatment regimens incorporating the CD20 monoclonal antibody rituximab have been evaluated. A phase II study from MDACC evaluated hyper-CVAD with or without rituximab in previously untreated patients with Ph-negative B-lineage ALL (n = 282; median age, 41 years; range, 13–83 years). Among the subgroup of patients with CD20-positive ALL who were treated with hyper-CVAD combined with rituximab, the 3-year CR duration and OS rates were 67% and 61%, respectively. In addition, among the younger patients (age < 60 years) with CD20-positive disease, modified hyper-CVAD plus rituximab resulted in a significantly improved CR
duration (70% vs 38%; \(P<.001\)) and OS rate (75% vs 47%; \(P=.003\)) compared with the standard hyper-CVAD regimen without rituximab.\[^{165}\] No significant differences in outcomes with the addition of rituximab were noted for the subgroup of patients with CD20-negative disease. Notably, older patients (aged \(\geq 60\) years) with CD20-positive disease demonstrated higher rates of MRD negativity with the inclusion of rituximab; however, this did not translate into a survival benefit, again largely due to increased mortality in CR. It is worth noting that this high rate of death in CR for older patients may relate to anthracycline intensification as opposed to rituximab.\[^{166}\]

### Linker 4-Drug Regimen

Linker et al\[^{167}\] evaluated an intensified chemotherapy regimen that incorporated a 4-drug induction regimen (comprising vincristine, daunorubicin, prednisone, and asparaginase) with or without rituximab for CD-20-positive disease in adolescent and adult patients with ALL (\(n=84\); Ph-positive in 16%; median age, 27 years; range, 16–59 years). The 5-year EFS and OS rates for all patients were 48% and 47%, respectively. Among the patients who experienced a CR (93% of all patients), the 5-year EFS rate was 52%. The 5-year EFS rate was 60% for the sub-group of patients without high-risk features (\(n=53\)).\[^{167}\]

### Blinatumomab

Blinatumomab has shown promising clinical efficacy as a means of eradicating persistent MRD following upfront chemotherapy. In a multicenter, single-arm, phase II study, Topp et al\[^{168}\] 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 achieved MRD negativity before blinatumomab, or had experienced a hematologic CR with MRD \(\geq 10^{-4}\). After blinatumomab treatment, 16 of 20 evaluable patients were determined to be MRD-negative at a detection threshold of \(10^{-4}\).\[^{168}\] After a median follow-up of 33 months, the hematologic RFS of the evaluable cohort was 61%.\[^{168}\] Gökbüget et al\[^{170}\] examined the efficacy of blinatumomab in an expanded cohort (\(n=116\)) using a higher threshold for MRD positivity (hematologic CR with MRD \(\geq 10^{-3}\)). After one 28-day cycle of blinatumomab, 88 of 113 evaluable patients achieved a complete MRD response, and the RFS rate at 18 months was 54%.\[^{170}\] In both of these trials, most patients achieving MRD negativity after blinatumomab proceeded to allogeneic HCT, establishing blinatumomab as an effective “bridge to transplant” in MRD-positive patients. Subsequent studies of blinatumomab evaluated its ability to induce CR (including rapid MRD-negative responses) in patients with R/R B-precursor ALL.\[^{171–173}\] In March 2018, the FDA approved blinatumomab use for the treatment of adult and pediatric patients with B-cell precursor ALL in first or second CR with MRD defined as disease \(\geq 0.1\) (see “Treatment of Relapsed Ph-Negative ALL,” [next section] for discussion of studies related to blinatumomab use in R/R B-ALL).

### Treatment of Relapsed Ph-Negative ALL

Despite major advances in the treatment of childhood ALL, approximately 20% of pediatric patients experience relapse after initial CR to frontline treatment regimens.\[^{174–176}\] Among those who experience relapse, only approximately 30% experience long-term remission with subsequent therapies.\[^{177–179}\] Based on a retrospective analysis of historical data from COG studies (for patients enrolled between 1998 and 2002; \(n=9585\)), early relapse (<18 months from diagnosis) was associated with very poor outcomes, with an estimated 5-year survival (from time of relapse) of 21%.\[^{174}\] For cases of isolated bone marrow relapse, the 5-year survival estimates among early (\(n=412\)), intermediate (\(n=324\)), and late (\(n=387\)) relapsing disease were 11.5%, 18.0%, and 43.5%, respectively (\(P<.0001\)). Intermediate relapse was defined as relapse occurring between 18 and 36 months from time of diagnosis; late cases were defined as relapse occurring 36 months or more from time of diagnosis. For cases of isolated CNS relapse, the 5-year survival estimates among early (\(n=175\)), intermediate (\(n=180\)), and late (\(n=54\)) relapsing disease were 43.5%, 68.0%, and 78.0%, respectively (\(P<.0001\)).\[^{174}\] Based on multivariate analysis (adjusted for both timing and site of relapse), age (>10 years), presence of CNS disease at diagnosis, male gender, and T-cell lineage disease were found to be significant independent predictors of decreased survival after relapse.\[^{174}\] In a separate analysis of data from one of the above COG studies (CCG-1952), the timing and site of first relapse were significantly predictive of EFS and OS outcomes, even among the patients with standard-risk ALL (\(n=347\); based on NCI criteria: aged 1 to <10 years and WBC count \(<50 \times 10^9/L\)).\[^{180}\] Early bone marrow relapse (duration of first CR <36 months) was associated with significantly shorter estimated 3-year EFS (30% vs 44.5%; \(P=.002\)) and OS (35% vs 58%; \(P=.001\)) rates compared with late bone marrow relapse.\[^{180}\] Similarly, early isolated extramedullary relapse (duration of first CR <18 months) was associated with significantly shorter estimated 3-year EFS (37% vs 71%; \(P=.01\)) and OS (55% vs 81.5%; \(P=.039\)) rates compared with late extramedullary relapse. In a multivariate regression analysis, early bone marrow and extramedullary relapse were independent predictors of poorer EFS outcomes.\[^{180}\]

Data from patients with disease relapse after frontline therapy in the MRC UKALL XII/ECOG E2993 study and PETHERMA studies showed that the median OS after relapse was only 4.5 to 6 months; the 5-year OS rate was 7%–10%.\[^{180}\] Approximately 20%–30% of patients experience a second CR with second-line therapies.\[^{91,93}\] Factors
predictive of more favorable outcomes after subsequent therapies included younger age and a first CR duration of more than 2 years. Among younger patients (aged <30 years) whose disease relapsed after experiencing a first CR duration longer than 2 years with frontline treatment in PETHEMA trials, the 5-year OS rate from the time of first relapse was 38%.134

### Hematopoietic Cell Transplant

HCT is the only potentially curative modality for R/R ALL. Based on findings from evidence-based review of the published literature, the American Society for Blood and Marrow Transplantation guidelines recommend HCT over chemotherapy alone for adult patients with ALL experiencing a second CR. Several studies have shown that for AYA patients in second CR, allogeneic HCT may improve outcomes, particularly for patients who have early bone marrow relapse or have other high-risk factors.133,170,185 Seemingly contradictory data were reported in the COG CCG-1952 study that showed prognosis after early bone marrow relapse in patients with standard-risk ALL (aged 1 to <10 years and WBC count <50 × 10^9/L) remained poor with no apparent advantage of HCT, regardless of timing (i.e., early or late) of bone marrow relapse. However, data were not available on the conditioning regimen used for HCT in this study for comparison with other trials. The UKALLXII/ECOG2993 trial (n = 609; age range, 15–60 years) examined the efficacy of transplantation after relapse in a subgroup of patients with relapsed ALL who had not received prior transplant. Patients treated with HCT demonstrated a superior OS at 5 years compared with those treated with chemotherapy alone.180 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%). Response to salvage therapy prior to HCT may also predict outcome. One retrospective study has shown 3-year OS and EFS estimates of 69% and 62% (respectively) for patients in second or later MRD-negative remission at the time of HCT, similar to the outcomes of those who underwent HCT in MRD-negative first remission at the same center.185

### 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 patients with R/R B-cell precursor ALL (n = 25). Blinatumomab was approved by the FDA based on data from a large phase II confirmatory study of 189 patients with R/R Ph-negative B-ALL that demonstrated a CR or CR with incomplete platelet recovery (CRp) in 43% of patients within the first 2 cycles of treatment.172,187 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). The OS was longer in the blinatumomab group, with median OS at 7.7 months, compared with the standard chemotherapy group, with median OS at 4.0 months (95% CI, 0.55–0.93; P < .01). 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). Of note, prespecified subgroup analyses of patients with high bone marrow count (≥50%) at relapse demonstrated lower blinatumomab-mediated median survival and remission rates.171

There are significant and unique side effects to blinatumomab treatment compared with the current standard-of-care regimens. 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. CRS typically occurs within the first 2 days after initiation of blinatumomab infusion. 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.

### Inotuzumab Ozogamicin

Clinical studies described earlier include patients with relapsed or refractory Ph-positive and Ph-negative ALL. For discussion of these studies, see “Treatment of Relapsed Ph-Positive ALL” (page 1091).

In a phase II study, the efficacy and safety of inotuzumab ozogamicin combined with low-intensity chemotherapy (mini-hyper-CVD) was evaluated in adults with R/R B-ALL (n = 59; median age, 35 years; range, 18–87 years). The response rate was 78%, with 35 of these patients achieving CR (59%). The overall MRD negativity rate among responders was 82%. With a median follow-up of 24 months, the median RFS and OS were 8 and 11 months, respectively. The 1-year RFS and OS rates were 40% and 46%, respectively. When using this regimen, the risk of veno-occlusive disease should be considered in patients with previous liver damage and...
CAR T Cells

One of the early treatments for patients with advanced ALL included adoptive cell therapy to induce a graft-versus-leukemia effect through allogeneic HCT or DLI. However, this method resulted in a significant risk of GVHD. To circumvent this issue, current advances are focused on the use of the patient’s own T cells to target the tumor. The generation of CAR T cells to treat ALL is a significant advancement in the field.\(^\text{134,191,192}\) CAR T-cell therapy relies on the genetic manipulation of a patients’ T-cells to generate a response against a leukemic cell-surface antigen, most commonly CD19.\(^\text{135}\) 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.\(^\text{135}\) The manufacture of CAR T cells requires ex vivo viral transduction, activation, and expansion over several days to produce a sufficient cell number to engender disease response.\(^\text{193}\) Following infusion, debulking of tumors occurs in less than a week and these 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 relapsed or refractory ALL. One of the first CAR constructs to be investigated, termed 19-28z—which links the CD19 binding receptor to the costimulatory protein CD28—demonstrated an overall CR in 14 of 16 patients with relapsed or refractory B-ALL after infusion with CAR T cells.\(^\text{194}\) This average remission rate is significantly improved compared with the average remission rate for patients receiving standard-of-care chemotherapy following relapse (88% vs approximately 30%).\(^\text{30,194–196}\) Furthermore, 7 of 16 patients were able to receive an allogeneic HCT, suggesting that CAR T cells may provide a bridge to transplant.\(^\text{194}\) No relapse has been seen in patients who had allogeneic HCT (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.\(^\text{197}\) 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) and subsequent allogeneic HCT did not appear to improve survival.\(^\text{197}\) In contrast, data in children and young adults treated on another clinical trial at the National Institutes of Health/National Cancer Institute with a similar CAR construct suggested consolidative allogeneic HCT post-CAR T-cell therapy might be associated with superior outcomes (2-year cumulative incidence of relapse posttransplant, 9.5%; 5-year event-free survival posttransplant, 62%).\(^\text{198}\) The ZUMA-3 clinical trial phase II results using the CAR T-cell product CTL019 (brexucabtagene autoleucel) also showed promising efficacy in adults with R/R ALL, by demonstrating MRD-negative CR in 76% of patients, with a median duration of remission of 12.8 months, a median relapse-free survival of 11.6 months, and a median overall survival of 18.2 months.\(^\text{199}\) KTE-X19 is currently being evaluated in children and young adults with R/R ALL.

Other CD19-targeted constructs have been investigated, some comprising an alternative costimulatory protein, 4-1BB have shown similar results to the 19-28z CAR T cells in terms of overall CR.\(^\text{200}\) Relevant in this context are data from the ELIANA trial of CTL019 (tisagenlecleucel) in 75 children and young adults with R/R B-ALL, which demonstrated an overall remission rate of 81% within 3 months of infusion, all of which were notably MRD negative.\(^\text{201}\) These results led to the approval of CTL019 by the FDA in August 2017 for the treatment of patients up to age 25 years (aged <26 years) with R/R precursor B-ALL. The efficacy of CTL019 in children and young adults with R/R B-ALL in the nontrial setting was recently confirmed using registry data from the Center for International Blood and Marrow Transplant Research (CIBMTR). This retrospective analysis showed morphologic CR in 85% of patients.\(^\text{202}\) MRD negativity was reported in 99% of CR patients with available data. A comparable proportion of patients experienced durable responses at 12 months in the CIBMTR cohort compared with patients treated on the ELIANA clinical trial (61% and 67%, respectively). At the last update of the ELIANA data at the 2019 American Society of Transplantation and Cellular Therapy (ASTCT) Annual Meeting (median follow-up, 24 months), the median duration of remission and overall survival was not reached and the 24-month relapse-free survival probability in responders was 62%.
Survival probability curves plateaued after 1 year. Consolidation with allo-HCT after CT019 was reported in only 9% of CR patients. These updated results suggest treatment with CT019 in children and young adults with R/R B-ALL could be curative in a subset of patients in the absence of consolidative allo-HCT.203

As with blinatumomab, T-cell and CAR T-cell activation can be accompanied by severe CRS and neurologic toxicity (immune effector cell associated neurotoxicity syndrome or ICANS), as well as infectious risks—though treatment-related mortality remains low.201 Although side effects from CAR T cells can be severe, they are reversible in most cases. CRS is clinically characterized by high fever, hypotension, tachycardia, and hypoxia; ICANS includes delirium, aphasia, headaches, tremor, focal deficits, and cerebral edema. Higher CRS and ICANS severity have been reported in B-ALL patients compared with non-Hodgkin lymphoma patients after CD19 CAR T-cell therapy.204 It is recommended to evaluate CRS and ICANS severity using the ASTCT consensus criteria.205 Tocilizumab (interleukin-6 receptor antagonist) and corticosteroids are the cornerstone of CRS and ICANS management. Expert consensus clinical guidelines were recently published by the Society of Immunotherapy of Cancer to guide toxicity management.206

**Nelarabine**

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 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).177 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 adults with R/R T-ALL or T-cell lymphoblastic leukemia in a phase II study (n = 39; median age, 34 years; range, 16–66 years; median 2 prior regimens; T-ALL, n = 26).207 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.207

There are limited studies of nelarabine combination regimens in adults with R/R T-ALL. In a study by Commander et al, pediatric patients with R/R T-ALL (n = 7; range, 1–19 years) were treated with nelarabine, etoposide and cyclophosphamide.208 In addition, all patients received intrathecal prophylaxis with methotrexate or triple intrathecal therapy with methotrexate, cytarabine, and hydrocortisone. All patients experienced a CR after 1 or 2 courses of therapy. The most common adverse events attributed to nelarabine were grade 2 and 3 sensory and motor neuropathy and musculoskeletal pain.208

In phase I of the NECTAR trial, pediatric patients with R/R T-ALL and T-LL (range, 1–21 years) were also treated with nelarabine, etoposide and cyclophosphamide.209 Of nine evaluable T-ALL patients, there were 2 CRs, 1 partial CR, and 1 CR in the bone marrow/PR in an extramedullary site for a response rate of 44%.209

**Augmented Hyper-CVAD**

A phase II study from the MDACC evaluated an augmented hyper-CVAD regimen (that incorporated asparaginase, intensified vincristine, and intensified dexamethasone) as therapy in adults with R/R ALL (n = 90; median age, 34 years; range, 14–70 years; median 1 prior regimen).210 Among evaluable patients (n = 88), the CR rate was 47%; an additional 13% experienced a CRp and 5% experienced a partial remission. The 30-day mortality rate was 9% and median remission duration was 5 months. The median OS for all evaluable patients was 6.3 months; median OS was 10.2 months for patients who experienced a CR. In this study, 32% of patients were able to proceed to HCT.210

**Vincristine Sulfate Liposomal Injection**

Vincristine sulfate liposome injection (VSLI) is a novel nanoparticle formulation of vincristine encapsulated in sphingomyelin and cholesterol liposomes; the liposome encapsulation prolongs the exposure of active drug in the circulation and may allow for delivery of increased doses of vincristine without increasing toxicities.211,212 VSLI was evaluated in an open-label, multicenter, phase II study in adult patients with Ph-negative ALL (n = 65; median age, 31 years; range, 19–83 years) in second or greater relapse, or with disease that progressed after 2 or more prior lines of therapy (RALLY study).196 The CR (CR + CRi) rate with single-agent VSLI was 20%. The median duration of CR was 23 weeks (range, 5–66 weeks) and the median OS for all patients was 20 weeks (range, 2–94 weeks); median OS for patients achieving a CR was 7.7 months.196 The incidence of early induction death (30-day mortality rate) was 12%,196 These outcomes appeared favorable compared with published single-center historical data in patients with Ph-negative ALL treated with other agents at second relapse (n = 56; CR rate, 4%; median OS, 7.5 weeks; early induction death, 30%).196,213 The most common grade 3 or greater treatment-related toxicities with VSLI included neuropathy (23%), neutropenia (15%), and thrombocytopenia (6%).196 Based on phase II data from the RALLY study, VSLI was given accelerated FDA approval in September 2012 for the treatment of adult
patients with Ph-negative B-ALL in second or greater relapse. Confirmation of benefit from phase III studies is pending.

**Clofarabine**

Clofarabine is a nucleoside analog approved for the treatment of pediatric patients (aged 1–21 years) with ALL that is relapsed or refractory after at least 2 prior regimens. In a phase II study of single-agent clofarabine in heavily pretreated pediatric patients with R/R ALL (n=61; median age, 12 years; range, 1–20 years), the response rate (CR + CRp) was 20%. Single-agent clofarabine in this setting was associated with severe liver toxicities (generally reversible) and frequent febrile episodes including grade 3 or 4 infections and febrile neutropenia. Phase II studies evaluating the combination of clofarabine with cyclophosphamide and etoposide in pediatric patients with R/R ALL have resulted in response rates ranging from 44% to 52%. This combination has been associated with prolonged and severe myelosuppression, febrile episodes, severe infections (including sepsis or septic shock), mucositis, and liver toxicities including fatal veno-occlusive disease (the latter occurring in the postallogeneic HCT setting).

There are limited studies of clofarabine combination regimens in adults with R/R disease. In a study by Miano et al, pediatric patients with R/R ALL (n=24; median age, 7.6 years; range, 1–20 years) were treated with clofarabine, etoposide, and cyclophosphamide, and 42% (10 of 24) of patients responded to treatment, with a 24-month OS rate of 25%. In a study from GRAALL, adult patients with R/R ALL (n=55) were treated with clofarabine in combination with conventional chemotherapy (cyclophosphamide [ENDEVOL cohort; median age, 53 years; range, 18–78 years], or a more intensive regimen with dexamethasone, mitoxantrone, etoposide, and PEG-asparaginase [VANDEVOL cohort; median age, 34 years; range, 19–67 years]). Patients in the ENDEVOL cohort achieved a CR of 50% (9 of 18) and patients in the VANDEVOL cohort yielded a CR rate of 41% (15 of 37); the median OS was 6.5 months after a median follow-up of 6 months. The most common grade 3 or 4 toxicities included infection (58%) and liver toxicities (24%), with an early death rate of 11%. Because the use of clofarabine-containing regimens require close monitoring and intensive supportive care measures, patients should only be treated in centers with expertise in the management of ALL, preferably in the context of a clinical trial.

**MOpAD Regimen**

A single-arm trial evaluating the efficacy of the MOpAD regimen (methotrexate, vincristine, L-asparaginase, and dexamethasone) in newly diagnosed adults with ALL (n=55) demonstrated a CR rate of 76% with a median CR duration of over 12 months. A phase II trial incorporated a new PEGylated formulation of L-asparaginase due to improved tolerability, and examined the safety and efficacy of the MOpAD regimen (methotrexate, vincristine, PEG-L-asparaginase, and dexamethasone) in adults with relapsed or refractory ALL (n=37). For patients with Ph-positive ALL, TKIs (ie, imatinib, dasatinib, nilotinib) were added to the regimen and if patients had CD20-positive B-ALL, rituximab was added to the regimen. The CR and ORR rates were 28% and 39%, respectively, with a median duration of response of 4.3 months. Patients with Ph-positive ALL had CR and ORR rates of 50% and 67%, respectively. This regimen may be considered in patients who have received a maximal dose of anthracycline and have cardiac dysfunction and limited performance status.

**TKIs**

Studies evaluating other novel TKIs in targeting specific genetic subtypes have been evaluated for the treatment of R/R T-ALL disease. Although daratumumab has efficacy in its application for MRD, it has been reported to have potential preclinical benefit in T-ALL with positive CD38 expression. The use of selective BCL2 inhibitor, venetoclax, has been retrospectively analyzed in the treatment of R/R T-ALL. In this analysis, 60% of patients receiving venetoclax plus various chemotherapeutic agents such as hyper-CVAD, nelarabine, or decitabine, achieved remission in marrow blasts, with a median overall survival of 7.7 months. Proteasome inhibition with the use of bortezomib in combination with chemotherapeutic agents has been suggested to improved relapse response rates in T-ALL patients. In a phase II COG study, patients with ALL were treated with reinduction chemotherapy plus bortezomib. Relapsed T-ALL patients showed a complete response rate of 68%, with end of induction MRD significantly predicting survival.

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### Individual Disclosures for the NCCN Acute Lymphoblastic Leukemia Panel

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The NCCN Guidelines Staff have no conflicts to disclose.

*The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty: Amanda Prasopwolosko, DO; Bristol-Myers Squibb Company; Cura Therapeutics; Fate Therapeutics; Intella Therapeutics; Johnson & Johnson; Karyopharm Therapeutics; Moderna, and Novavax.