Abstract

Treatment of acute lymphoblastic leukemia (ALL) continues to advance, as evidenced by the improved risk stratification of patients and development of newer treatment options. Identification of ALL subtypes based on immunophenotyping and cytogenetic and molecular markers has resulted in the inclusion of Philadelphia-like ALL and early T-cell precursor ALL as subtypes that affect prognosis. Identification of Ikaros mutations has also emerged as a diagnostic factor. In addition to improved prognostication, treatment options for patients with ALL have expanded, particularly with regard to relapsed/refractory ALL. Continued development of second-generation tyrosine kinase inhibitors and the emergence of immunotherapy, including blinatumomab and chimeric antigen receptor T-cell therapy, have improved survival. Furthermore, incorporation of minimal residual disease (MRD) monitoring has shown insight into patient outcomes and may lead to treatment modification or alternative treatment strategies in select populations. This excerpt focuses on the sections of the ALL guidelines specific to clinical presentation and diagnosis, treatment of relapsed/refractory ALL, and incorporation of MRD monitoring. To view the most recent complete version of these guidelines, visit NCCN.org. (J Natl Compr Canc Netw 2015;13:1240–1279)

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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

Please Note

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Disclosures for the NCCN 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 1279. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.
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 (AYA) 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 manuscript highlights only a portion of the NCCN Guidelines for ALL, including immunophenotyping, cytogenetic and molecular subtypes, the treatment of relapsed/refractory ALL, and the role of minimal residual disease (MRD) evaluation. Please refer to NCCN.org for the complete guidelines.

ALL is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs.\textsuperscript{1} The age-adjusted incidence rate of ALL in the United States is 1.77 per 100,000 individuals per year,\textsuperscript{2} with approximately 6250 new cases and 1450 deaths estimated in 2015.\textsuperscript{3} The median age at diagnosis for ALL is 14 years,\textsuperscript{4} with 58.8% of patients diagnosed at younger than 20 years of age.\textsuperscript{5} In contrast, 25.5% of cases are diagnosed at 45 years or older, and only approximately 11% of patients are diagnosed at 65 years or older.\textsuperscript{5} ALL represents 75% to 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.\textsuperscript{1,6}
The diagnosis of ALL generally requires demonstration of ≥20% bone marrow lymphoblasts upon hematopathology review of bone marrow aspirate and biopsy materials, which includes:

- Morphologic assessment of Wright-Giemsa stained bone marrow aspirate smears, and H&E stained core biopsy and clot sections
- Comprehensive flow cytometric immunophenotyping

**GENETIC CHARACTERIZATION**

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

- Karyotyping of G-banded metaphase chromosomes (cytogenetics)
- Interphase fluorescence in situ hybridization (FISH) testing including probes capable of detecting the major recurrent genetic abnormalities
- Reverse transcriptase-polymerase chain reaction (RT-PCR) testing for fusion genes (eg, BCR-ABL). Other fusions that describe Ph-like ALL

Additional optional tests include:

- Flow cytometric DNA index/ploidy testing (additional assessment for hyperdiploidy and hypodiploidy)

**CLASSIFICATION**

Together, these studies allow determination of the World Health Organization (WHO) ALL subtype and cytogenetic risk group.

Strongly recommend that patients be treated in specialized centers.
WORKUP

- History and Physical (H&P)
- Complete blood count (CBC), platelets, differential, chemistry profile
- Disseminated intravascular coagulation (DIC) panel: d-dimer, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT)
- Tumor lysis syndrome (TLS) panel: lactate dehydrogenase (LDH), uric acid, K, Ca, Phos (See Tumor Lysis Syndrome in the NCCN Guidelines for Non-Hodgkin’s Lymphomas, available at NCCN.org)
- CT/MRI of head, if neurologic symptoms
- Lumbar puncture (LP)
  - See Evaluation and Treatment of Extramedullary Involvement (ALL-C)
  - Consider intrathecal (IT) chemotherapy
- CT of chest (for patients with T-cell ALL [T-ALL])
- Testicular exam
- Infection evaluation:
  - Screen for active infections if febrile or for symptomatic opportunistic infections
  - Initiate empirical treatment, as appropriate (See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections, available at NCCN.org)
- Echocardiogram or cardiac scan should be considered in all patients, since anthracyclines are important components of ALL therapy, but especially in patients with prior cardiac history and prior anthracycline exposure of clinical symptoms suggestive of cardiac dysfunction
- Central venous access device of choice
- Human leukocyte antigen (HLA) typing (except for patients with a major contraindication to hematopoietic cell transplant [HCT])
- In patients with poor-risk features who lack a sibling donor, consider early evaluation and search for an alternative donor

RISK STRATIFICATION

Ph+ ALL (AYA) → See Treatment (ALL-3)
Ph+ ALL (Adult) → See Treatment (ALL-4)
Ph- ALL (AYA) → See Treatment (ALL-5)
Ph- ALL (Adult) → See Treatment (ALL-6)

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

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

Timing of LP should be consistent with the chosen treatment regimen. Pediatric-inspired regimens typically include LP at the time of diagnostic workup. The panel recommends that LP, if performed, be done concurrently with initial IT therapy.
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Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

### Treatment Induction

**Ph+ ALL (AYA)** (aged 15-39 y)
- Clinical trial
- Chemotherapy + tyrosine kinase inhibitor (TKI)

**Monitoring for minimal residual disease (MRD)**
- Complete response (CR)
- Less than CR

**Consolidation Therapy**
- Allogeneic HCT, if a donor is available
- If allogeneic HCT is not available, continue multiagent chemotherapy + TKI

**Risk Stratification**

**Patients <65 years of age or with no substantial comorbidities**
- Clinical trial
- TKI + corticosteroids
- TKI + chemotherapy

**Patients 65 years of age or with substantial comorbidities**
- CR
- Continue TKI ± corticosteroids
- Continue TKI ± chemotherapy

### Additional Considerations

- 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 senior adult patients with ALL, see the NCCN Guidelines for Older Adult Oncology, available at NCCN.org.

- ALL treatment regimens include CNS prophylaxis.
- See Principles of Chemotherapy (ALL-D).
- See Discussion section for use of different TKIs in front-line therapy.
- See Response Criteria (ALL-E).
- See Minimal Residual Disease Assessment (ALL-F).

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RISK STRATIFICATION

- Patients <65 years of age or with no substantial comorbidities
  - Clinical trial or Chemotherapy + TKI
  - CR \( \rightarrow \) Monitoring for MRD

- Patients ≥65 years of age or with substantial comorbidities
  - Clinical trial or TKI + corticosteroids or TKI + chemotherapy
  - CR \( \rightarrow \) Less than CR

Ph+ ALL (Adult) (aged ≥40 y)

- Clinical trial or Chemotherapy + TKI
  - CR \( \rightarrow \) Monitoring for MRD

- Less than CR \( \rightarrow \) See Relapse/Refractory Disease (ALL-7)

CONSOLIDATION THERAPY

- Allogeneic HCT, if a donor is available or if an allogeneic HCT donor is not available, continue multiagent chemotherapy + TKI
  - Consider post-HCT TKI

- Maintenance therapy + TKI \( \rightarrow \) See Surveillance (ALL-7)

- Maintenance therapy + TKI \( \rightarrow \) See Surveillance (ALL-7)

- Less than CR \( \rightarrow \) See Relapse/Refractory Disease (ALL-7)

- See Response Criteria (ALL-E).

- See Minimal Residual Disease Assessment (ALL-F).

- For additional considerations in the management of senior adult patients with ALL, see the NCCN Guidelines for Older Adult Oncology, available NCCN.org.

- Consider dose modifications appropriate for patient age and performance status.

- Allogeneic HCT may be considered based on performance status, comorbidities, availability of appropriate transplant donor, and transplant center expertise in treating older patients with allogeneic HCT.

**Footnotes:**

- 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.
- All ALL treatment regimens include CNS prophylaxis.
- See Principles of Chemotherapy (ALL-D).
- See Discussion section for use of different TKIs in front-line therapy.
- See Response Criteria (ALL-E).
- See Minimal Residual Disease Assessment (ALL-F).
- For additional considerations in the management of senior adult patients with ALL, see the NCCN Guidelines for Older Adult Oncology, available NCCN.org.
- Consider dose modifications appropriate for patient age and performance status.
- Allogeneic HCT may be considered based on performance status, comorbidities, availability of appropriate transplant donor, and transplant center expertise in treating older patients with allogeneic HCT.
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RISK STRATIFICATION

TREATMENT INDUCTION

CONSOLIDATION THERAPY

Ph- ALL (AYA) (aged 15-39) Ph- ALL (Adult) Ph- ALL (Pediatric)

Clinical trial or Pediatric-inspired multiagent chemotherapy

CRp

Monitoring for MRD

Continue multiagent chemotherapy (especially MRD+)

Consider allogeneic HCT if a donor is available (especially MRD+, high WBC, or poor-risk cytogenetics)

Maintenance therapy

See Surveillance (ALL-7)

See Relapse/Refractory Disease (ALL-7)

Cytogenetic risk groups are defined as follows:

- **Good risk**: Hypodiploidy (51-65 chromosomes and/or DNA index >1.16; cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome); t(12;21)(p13;q22); ETV6-RUNX1; Poor risk: Hypodiploidy (<44 chromosomes and/or DNA index <0.81); t(v;11q23); MLL rearranged; t(9;22)(q34;q11.2); BCR-ABL (defined as high risk in the pre-TKI era); Complex karyotype (5 or more chromosomal abnormalities).
- **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 Oncology, available at NCCN.org.
- **All ALL treatment regimens include CNS prophylaxis**.
- **See Principles of Chemotherapy (ALL-D)**.
- **See Minimal Residual Disease Assessment (ALL-F)**.
- **See Response Criteria (ALL-E)**.
- **See Principles of Chemotherapy (ALL-D)**. All regimens include induction/delayed intensification (especially for pediatric-inspired regimens) and maintenance therapy.
- **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.**

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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### Risk Stratification

Cytogenetic risk groups are defined as follows:

- **Good risk**: Hyperdiploidy (51-65 chromosomes and/or DNA index >1.16; cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome); t(12;21)(p13;q22): ETV6-RUNX1;
- **Poor risk**: Hypodiploidy (<44 chromosomes and/or DNA index <0.81); t(v;11q23): MLL rearranged; t(9;22)(q34;q11.2): BCR-ABL (defined as high risk in the pre-TKI era); Complex karyotype (5 or more chromosomal abnormalities).

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.

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### Treatment Induction

**Ph- ALL (Adult)** (aged 15-39)

- Patients <65 years of age or patients with no substantial comorbidities:
  - Clinical trial or Multiagent chemotherapy or Corticosteroids
  - CR\(_p\) → Monitoring for MRD\(_q\)
- Patients ≥65 years of age or patients with substantial comorbidities:
  - Clinical trial or Multiagent chemotherapy or Corticosteroids
  - CR\(_p\) → Chemotherapy \(n,u\)

**See Minimal Residual Disease Assessment (ALL-F)**.

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### Consolidation Therapy

- Continue multiagent chemotherapy \(n\) (especially MRD-)
- Less than CR\(_p\) → See Relapse/Refractory Disease (ALL-7)
- See Surveillance (ALL-7)

**Consider allogeneic HCT if a donor is available (especially MRD+, high WBC, or poor risk cytogenetics)**

**Maintenance therapy**

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**Cytogenetic risk groups are defined as follows:**

- **Good risk**: Hyperdiploidy (51-65 chromosomes and/or DNA index >1.16; cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome); t(12;21)(p13;q22): ETV6-RUNX1;
- **Poor risk**: Hypodiploidy (<44 chromosomes and/or DNA index <0.81); t(v;11q23): MLL rearranged; t(9;22)(q34;q11.2): BCR-ABL (defined as high risk in the pre-TKI era); Complex karyotype (5 or more chromosomal abnormalities).

**For additional considerations in the management of AYA patients with ALL, see the NCCN Guidelines for Adolescent and Young Adult Oncology, available at NCCN.org.**

**Allogeneic HCT may be considered based on performance status, comorbidities, availability of appropriate transplant donor, and transplant center expertise in treating older patients with allogeneic HCT.**

**For further information, see Principles of Chemotherapy (ALL-D).**

**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 is less firmly established for adults than for the pediatric population.**
### SURVEILLANCE

Year 1 (every 1–2 months):
- Physical exam, CBC with differential every month
- Liver function tests (LFTs) every 2 months until normal
- Bone marrow aspirate, cerebrospinal fluid (CSF), and echocardiogram as indicated
  - If bone marrow aspirate is done:
    Comprehensive cytogenetics, FISH, flow cytometry, and consideration of molecular tests

Year 2:
- Physical exam including testicular exam, CBC with differential every 3 months
- Physical exam including testicular exam, CBC with differential every 6 months or as indicated

Refer to Survivorship recommendations in the NCCN Guidelines for Adolescent and Young Adult Oncology, available at NCCN.org. Refer to the ALL Long-term Follow-up Guidelines from Children's Oncology Group (COG): http://www.survivorshipguidelines.org/

### RELAPSE/REFRACTORY DISEASE

<table>
<thead>
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<th>Ph+ ALL (AYA &amp; Adult)</th>
<th>Consider ABL gene mutation testing*</th>
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<td>Consider clinical trial</td>
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### TREATMENT

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<th>Relapse/refractory YEAR 3+</th>
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<td>Consider clinical trial</td>
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<td>or Allogeneic HCT&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>or Chemotherapy&lt;sup&gt;bb,dd&lt;/sup&gt;</td>
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*See Discussion section for use of different TKIs in this setting.

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

†Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.

‡See NCCN Guidelines for Palliative Care, available at NCCN.org.

See Treatment Options Based on BCR-ABL Kinase Domain Mutation Status (ALL-D 3 of 4).

See Principles of Chemotherapy (ALL-D 3 of 4). Nelarabine is available for patients with relapsed T-ALL/lymphoblastic lymphoma. Clofarabine is available for patients age ≤21 y with relapsed or refractory ALL after at least 2 prior regimens. Vincristine sulfate liposome injection is available for adult patients with Ph- ALL in ≥ second relapse or disease progression after ≥2 therapies.

For patients with relapsed disease after allogeneic HCT, a second allogeneic HCT and/or donor lymphocyte infusion (DLI) can be considered.

For AYA patients in late relapse (>3 years from initial diagnosis), consider treatment with the same induction regimen (see ALL-D 2 of 4).
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TYPICAL IMMUNOPHENOTYPE BY MAJOR ALL SUBTYPES

The initial immunophenotyping panel should be sufficiently comprehensive to establish a leukemia-associated phenotype (LAP) that may include expression of non-lineage antigens. These LAPs are useful in classification, particularly mixed-lineage leukemias, and as a signature for MRD detection.

B-ALL, not otherwise specified: CD10+, CD19+, CD79a+, cCD22+, sCD22+, CD24+, PAX5+, TdT+, variable CD20, variable CD34
• Early precursor B-ALL (pro-B-ALL): CD10-, CD19+, cCD79a+, cCD22+, TdT+
• Common B-ALL: CD10+
• Precursor B-ALL (pre-B-ALL): cytoplasmic µ+, slg-, CD10+/-

B-ALL with recurrent genetic abnormalities:
• Hyperdiploidy (DNA index >1.16; 51–65 chromosomes without structural abnormalities): CD10+, CD19+, CD34+, CD45-
• Hypodiploidy (<44 chromosomes): CD10+, CD19+, CD34+
• t(9;22)(q34;q11.2); BCR-ABL1: CD10+, CD19+, TdT+, CD13+, CD33+, CD117-
• t(v;11q23); MLL rearranged: CD10-, CD19+, CD24-, CD15+
• t(12;21)(p13;q22); TEL-AML1: CD10+, CD19+, TdT+, CD13+, CD34+
• t(1;19)(q23;p13.3); E2A-PBX1: CD10+, CD19+, CD20 variable, CD34 +/-, cytoplasmic µ+
• t(5;14)(q31;q32); IL3-IGH: CD10+, CD19+

T-ALL: TdT+, variable for all of the following: CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD34
• Pro-T-ALL: cCD3+, CD7+, CD1a-, CD2-, CD4-, CD8-, CD34+/-
• Pre-T-ALL: cCD3+, CD7+, CD1a-, CD2-, CD4-, CD8-, CD34 +/-
• Cortical T-ALL: cCD3+, CD7+, CD1a+, CD2+, CD4+, CD8+, CD34-
• Medullary T-ALL: cCD3+, sCD3+, CD7+, CD1a-, CD2+, CD4+ or CD8+, CD34-
• ETP T-ALL: Lack of CD1a and CD8 expression, weak CD5 expression with less than 75% positive blasts, and expression of one or more of the following myeloid or stem cell markers on at least 25% of lymphoblasts: CD117, CD34, HLA-DR, CD13, CD33, CD11b, and/or CD65


1Criteria for classification of mixed phenotype acute leukemia (MPAL) should be based on the WHO 2008 criteria. Note that in ALL, myeloid-associated antigens such as CD13 and CD33 may be expressed, and the presence of these myeloid markers does not exclude the diagnosis of ALL.

**SUPPORTIVE CARE**

Best supportive care

- **Infection control** (See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections, available at NCCN.org)
  - Prophylactic anti-infectives
    - Antibacterial prophylaxis: consider fluoroquinolones
    - Antiviral prophylaxis: HSV prophylaxis; VZV prophylaxis for at least 1 year after HCT in transplant patients; and HBV prophylaxis for at least 6–12 months after HCT depending on HBV serology.
    - Cytomegalovirus (CMV) reactivation management: Consider CMV monitoring and pre-emptive therapy for all patients; for patients undergoing allogeneic HCT, CMV monitoring and pre-emptive therapy are strongly recommended until at least 6 months after transplantation.
    - Antifungal prophylaxis: Consider prophylaxis for all patients treated with chemotherapy; for patients undergoing allogeneic HCT, antifungal prophylaxis is strongly recommended until at least day 75 after transplantation.
  - Pneumocystis pneumonia (PCP) prophylaxis
  - Antifungal prophylaxis
    - Fever is defined as a single temperature ≥38.3 °C (101°F) or ≥38.0 °C (100.4°F) over a 1-hour period
  - IV antibiotics/inpatient admission
  - Acute TLS (See Tumor Lysis Syndrome in the NCCN Guidelines for Non-Hodgkin's Lymphomas, available at NCCN.org)
  - Pegaspargase Toxicity Management — see ALL-B 3 of 4 and ALL-B 4 of 4
  - Methotrexate and Glucarpidase
    - Consider use of glucarpidase if significant renal dysfunction and methotrexate levels are >10 microM beyond 42–48 h. Leucovorin remains a component in the treatment of methotrexate toxicity and should be continued for at least 2 days following glucarpidase administration. However, be aware that leucovorin is a substrate for glucarpidase, and therefore should not be administered within two hours prior to or following glucarpidase.
  - Steroid management
    - Acute side effects
      - Steroid-induced diabetes mellitus
        - Tight glucose control using sliding scale insulin to decrease infection complications
      - Steroid-induced psychosis and mood alteration
        - Consider dose reduction
      - Use of a histamine-2 antagonist or proton pump inhibitor (PPI)\(^1\) is recommended during steroid therapy
        - There are significant interactions between PPIs and TKIs regarding the bioavailability of certain bcr-abl TKIs with gastric acid suppression that should be considered.
    - Long-term side effects of corticosteroids
      - Osteonecrosis/avascular necrosis (also see Discussion)
      - Obtain vitamin D and calcium status and replete as needed
      - Consider radiographic evaluation with plain films or MRI or bone density study
  - Transfusions
    - Products should be irradiated
  - Use of granulocyte colony-stimulating factor (G-CSF)
    - Recommended for myelosuppressive blocks of therapy or as directed by treatment protocol
  - Hyperleukocytosis
    - Although uncommon in patients with ALL, symptomatic hyperleukocytosis may require emergent treatment (See Symptomatic Leukocytosis in the NCCN Guidelines for Acute Myeloid Leukemia, available at NCCN.org)
  - Antiemetics (See NCCN Guidelines for Antiemesis, available at NCCN.org)
    - Given as needed prior to chemotherapy and post chemotherapy
    - Routine use of corticosteroids as antiemetics are avoided
  - Gastroenterology
    - Consider starting a bowel regimen to avoid constipation
    - Docusate sodium daily
    - Laxatives promptly considered and used if symptoms arise
  - Nutritional support
    - Consider enteral or parenteral support for >10% weight loss
    - Palliative treatment for pain (See NCCN Guidelines for Cancer Pain, available at NCCN.org)

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\(^1\)There may be important drug interactions with methotrexate that need to be considered prior to initiation of methotrexate-based therapy.

ALL-B

1 and 2 of 4
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SUPPORTIVE CARE

Asparaginase Toxicity Management

- There are two formulations of asparaginase in clinical use: 1) Pegasparagase (PEG) and 2) asparaginase Erwinia chrysanthemi (Erwinia). PEG is a common component of therapy for children, adolescents, and young adults with ALL. Both agents can be given intramuscularly (IM) or intravenously (IV); the IV route is increasingly being used. The toxicity profile of both asparaginase products presents significant challenges in clinical management. The following guidelines are intended to help providers address these challenges.

Hypersensitivity, Allergy, and Anaphylaxis

- There is a significant incidence of hypersensitivity reactions with asparaginase products. Of particular concern are Grade 2 or higher systemic allergic reactions, urticaria or anaphylaxis, because these episodes are frequently associated with neutralizing antibodies.
- Erwinia is commonly used as a second-line agent in patients who have developed a systemic allergic reaction or anaphylaxis due to PEG hypersensitivity.
- Reactions that are NOT associated with neutralizing antibodies (and therefore are NOT an indication to switch to Erwinia) include: 1) local injection-site reactions after IM administration; 2) Grade 1 IV infusion-related allergic reactions (ie, transient flushing or rash, drug fever <38° C; intervention not indicated); and 3) Grade 1 urticaria.
- If pre-medication with antihistamines or steroids are used prior to PEG or Erwinia administration, consideration should be given to therapeutic drug monitoring (TDM) using commercially available asparaginase activity assays, since pre-medication may "mask" the systemic allergic reactions that often indicate the development of neutralizing antibodies.

Pancreatitis

- Permanently discontinue asparaginase in the presence of Grade 3 or 4 pancreatitis. In the case of Grade 2 pancreatitis (enzyme elevation or radiologic findings only), asparaginase should be held until these findings normalize and then resume.

Non-CNS Hemorrhage

- For Grade 2 or greater hemorrhage, hold asparaginase until Grade 1, then resume. Consider coagulation factor replacement. Do not hold for asymptomatic abnormal laboratory investigations.

Non-CNS Thromboembolism

- For Grade 2 or greater thromboembolic event, hold asparaginase until resolved and treat with appropriate antithrombotic therapy. Upon resolution of symptoms and antithrombotic therapy stable or completed, consider resuming asparaginase.

Intracranial Hemorrhage

- Discontinue asparaginase. Consider coagulation factor replacement. For Grade 3 or less, if symptoms/signs fully resolve, consider resuming asparaginase at lower doses and/or longer intervals between doses. For Grade 4, permanently discontinue asparaginase.

Cerebral Thrombosis, Ischemia, or Stroke

- Discontinue asparaginase. Consider antithrombotic therapy. For Grade 3 or less, if symptoms/signs fully resolve, consider resuming asparaginase at lower doses and/or longer intervals between doses. For Grade 4, permanently discontinue asparaginase.

Hyperglycemia

- Treat hyperglycemia with insulin as indicated. For Grade 3 or higher, hold asparaginase and steroids until blood glucose has been regulated with insulin, then resume.

Hypertriglycerideremia

- Treat hypertriglycerideremia as indicated. For Grade 4, hold asparaginase until normalized, then resume.

Hepatotoxicity (elevation in bilirubin, AST, ALT)

- For direct bilirubin ≤3.0 mg/dL, continue asparaginase. For direct bilirubin 3.1–5.0 mg/dL, hold asparaginase until ≤2.0 mg/dL, then resume. For direct bilirubin >5.0, either discontinue asparaginase or hold asparaginase until ≤2.0 mg/dL, then resume with very close monitoring.
- For Grade 3 AST or ALT elevation, hold until Grade 1, then resume. For Grade 4 AST or ALT elevation, hold until Grade 1. If resolution to Grade 1 takes 1 week or less, then resume. Otherwise, either discontinue or resume with very close monitoring.

ALL-B
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EVALUATION AND TREATMENT OF EXTRAMEDULLARY INVOLVEMENT

- Given the risks of neurotoxicity associated with central nervous system (CNS)-directed therapy, baseline and post-treatment comprehensive neuropsychological testing may be useful.
- The aim of CNS prophylaxis and/or treatment is to clear leukemic cells within sites that cannot be readily accessed by systemic chemotherapy due to the blood-brain barrier, with the overall goal of preventing CNS disease or relapse.
- Factors associated with increased risks for CNS leukemia in adults include mature B-cell immunophenotype, T-cell immunophenotype, high presenting WBC counts, and elevated serum LDH levels.¹ ²
- CNS involvement should be evaluated (by LP) at the appropriate timing:
  - Timing of LP should be consistent with the chosen treatment regimen.
  - Pediatric-inspired regimens typically include LP at the time of diagnostic workup.
  - The panel recommends that LP, if performed, be done concomitantly with initial IT therapy.
- Classification of CNS status:
  - CNS-1: No lymphoblasts in CSF regardless of WBC count.
  - CNS-2: WBC <5/mcL in CSF with presence of lymphoblasts.
  - CNS-3: WBC ≥5/mcL in CSF with presence of lymphoblasts.
  - If the patient has leukemic cells in the peripheral blood and the LP is traumatic and WBC ≥5/mcL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.
- All patients with ALL should receive CNS prophylaxis. Although the presence of CNS involvement at the time of diagnosis is uncommon (about 3%–7%), a substantial proportion of patients (>50%) will eventually develop CNS leukemia in the absence of CNS-directed therapy.
- CNS-directed therapy may include cranial irradiation, IT chemotherapy (eg, methotrexate, cytarabine, corticosteroids), and/or systemic chemotherapy (eg, methotrexate, cytarabine, mercaptopurine, pegaspargase).
- CNS leukemia (CNS-3 and/or cranial nerve involvement) at diagnosis typically warrants treatment with cranial irradiation of 18 Gy. The recommended dose of radiation, where given, is highly dependent on the intensity of systemic chemotherapy; thus, it is critical to adhere to a given treatment protocol in its entirety. The entire brain and posterior half of the globe should be included. The inferior border should be below C2.
- Note that areas of the brain targeted by the radiation field in the management of ALL are different from areas targeted for brain metastases of solid tumors.
- With the incorporation of adequate systemic chemotherapy (eg, high-dose methotrexate, cytarabine) and IT chemotherapy regimens (eg, methotrexate alone or with cytarabine and a corticosteroid, which constitutes the triple IT regimen), it may be possible to avoid the use of upfront cranial irradiation except in cases of overt CNS leukemia at diagnosis, and to reserve the use of irradiation for relapsed/refractory therapy settings.
- Adequate systemic therapy should be given in the management of isolated CNS relapse.
- Patients with clinical evidence of testicular disease at diagnosis that is not fully resolved by the end of the induction therapy should be considered for radiation to the testes in the scrotal sac, which is typically done concurrently with the first cycle of maintenance chemotherapy. Testicular total dose should be 24 Gy.


Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
Acute Lymphoblastic Leukemia, Version 2.2015

PRINCIPLES OF CHEMOTHERAPY

**Induction Regimens** for Ph-Positive ALL

Adult patients aged ≥40 years:
- TKIs + hyper-CVAD: imatinib or dasatinib; and hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate, and cytarabine
- TKIs + multiagent chemotherapy: imatinib; and daunorubicin, vincristine, prednisone, and cyclophosphamide
- TKIs (imatinib or dasatinib) + corticosteroids
- TKIs + vincristine + dexamethasone

Protocols for AYA patients aged 15–39 years:
- COG AALL-0031 regimen: vincristine, prednisone (or dexamethasone), and pegaspargase, with or without daunomycin; or prednisone (or dexamethasone) and pegaspargase with or without daunomycin; imatinib added during consolidation blocks
- TKIs + hyper-CVAD: imatinib or dasatinib; and hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate, and cytarabine
- TKIs + multiagent chemotherapy: imatinib; and daunorubicin, vincristine, prednisone, and cyclophosphamide

**Maintenance regimens**:
- Add TKIs (imatinib or dasatinib) to maintenance regimen
- Monthly vincristine/prednisone pulses (for 2–3 years). May include weekly methotrexate + daily 6-mercaptopurine (6-MP) as tolerated

**Induction Regimens** for Ph-Negative ALL

Adult patients aged ≥40 years:
- CALGB 8811 Larson regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide; for patients aged ≥60 years, reduced doses for cyclophosphamide, daunorubicin, and prednisone
- Linker 4-drug regimen: daunorubicin, vincristine, prednisone, and pegaspargase
- Hyper-CVAD +/- rituximab: hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine; with or without rituximab for CD20-positive disease
- MRC UKALLXII/ECOG2993 regimen: daunorubicin, vincristine, prednisone, and pegaspargase (induction phase I); and cyclophosphamide, cytarabine, and 6-mercaptopurine (induction phase II)

Pediatric-inspired protocols for AYA patients aged 15–39 years:
- GRAALL-0032 regimen: vincristine, prednisone (or dexamethasone), pegaspargase, and cyclophosphamide (patients aged <60 years)
- COG AALL-0434 regimen with nelarabine (for T-ALL): daunorubicin, vincristine, prednisone, and pegaspargase; nelarabine added to consolidation regimen (ongoing study)
- CCG-1961 regimen: daunorubicin, vincristine, prednisone, and pegaspargase (patients aged ≤21 years)
- PETHERA-ALL-96 regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide (patients aged ≤30 years)
- CALGB 10403 regimen: daunorubicin, vincristine, prednisone, and pegaspargase (ongoing study in patients aged <40 years)
- DFCI ALL regimen based on DFCI Protocol 00-01: doxorubicin, vincristine, prednisone, high-dose methotrexate, and pegaspargase (ongoing study in patients aged <50 years)
- USC ALL regimen based on CCG-1882 regimen: daunorubicin, vincristine, prednisone, and methotrexate with augmented pegaspargase (patients aged 18–57 years)

**Maintenance regimen**:
- Weekly methotrexate + daily 6-mercaptopurine + monthly vincristine/prednisone pulses (for 2–3 years)
PRINCIPLES OF CHEMOTHERAPY

Regimens for Relapsed/Refractory ALL

Ph-positive ALL:

- Dasatinib<sup>26,27,e</sup>
- Nilotinib<sup>28,f</sup>
- Bosutinib<sup>29,g</sup>
- Ponatinib<sup>30,h</sup>

The TKIs noted above may also be used in combination with any of the induction regimens noted on ALL-D 1 of 4 that were not previously given.

Ph-negative ALL:

- Clofarabine-containing regimens<sup>31,32</sup>
- Cytarabine-containing regimens<sup>33</sup>
- Alkylator combination regimens<sup>34</sup>
- Nelarabine (for T-ALL)<sup>35</sup>
- Augmented hyper-CVAD: hyper-fractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, and pegaspargase; alternating with high-dose methotrexate and cytarabine<sup>36</sup>
- Vincristine sulfate liposome injection (VSLI)<sup>37,38</sup>
- Blinatumomab (for B-ALL)<sup>39-41,i</sup>

<sup>4</sup>All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine, 6-mercaptopurine) and/or IT therapy (eg, IT methotrexate, IT cytarabine, triple IT therapy with methotrexate, cytarabine, corticosteroid).

<sup>6</sup>For patients with mutations Y253H, E255K, or F359V/C/I.

<sup>8</sup>For patients with mutations F317L/V/I/C, T315A, or V299L.

<sup>10</sup>For patients with mutations E255K, F317L/V/I/C, F359V/C/I, T315A, or Y253H.

<sup>12</sup>Ponatinib has activity against T315I mutations and is effective in treating patients with resistant or progressive disease on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). The FDA indications are for the treatment of adult patients with T315I positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) and for the treatment of adult patients with Ph+ ALL for whom no other TKI therapy is indicated. For details, see http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203469s007a008lbl.pdf.

<sup>14</sup>Blinatumomab may cause severe, life-threatening, or fatal adverse events, including cytokine release syndrome and neurologic toxicities. Understanding of the risk evaluation and mitigation strategy (REMS) program and/or experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instruction for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdose and overdose. For details, see http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails.

ALL-D

3 of 4
Regimens for Relapsed/Refractory ALL

Blinatumomab may cause severe, life-threatening, or fatal adverse events, including cytokine release syndrome and neurologic toxicities. Understanding the risks, including underdose and overdose. For details, see http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails.

For patients with mutations F317L/V/I/C, T315A, or V299L.

Blinatumomab (for B-ALL)

Vincristine sulfate liposome injection (VSLI)

pegaspargase; alternating with high-dose methotrexate and cytarabine

Augmented hyper-CV AD: hyper-fractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, and

Nelarabine (for T-ALL)

Clofarabine-containing regimens

For adult patients with T315I positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) and for the treatment of adult patients with Ph+ ALL who failed imatinib: results from a phase 3 study. Am J Hematol 2010;85:164-170.


Bosutinib safety and management of toxicity in leukemia patients with resistance or intolerance to imatinib and other tyrosine kinase inhibitors. Blood 2014;123:1309-1318.

Continued on next page

References


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PRINCIPLES OF CHEMOTHERAPY

References


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MINIMAL RESIDUAL DISEASE ASSESSMENT

MRD in ALL refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieved a CR by morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow.

MRD is an essential component of patient evaluation over the course of sequential therapy. If patient is not treated in an academic center, there are commercially available tests available for MRD assessment.

Studies in both children and adults with ALL have demonstrated the strong correlation between MRD and risks for relapse, as well as the prognostic significance of MRD measurements during and after initial induction therapy.

The minimal limit of assay sensitivity (to declare MRD negativity) should be <1 × 10^-6 (<0.01%) bone marrow mononuclear cells (MNCs). The concordance rate for detecting MRD between these methods is generally high. The combined or tandem use of both methods allows for MRD monitoring in all patients, thereby avoiding potential false-negative results.

Timing of MRD assessment:
- Upon completion of initial induction.
- Additional time points may be useful depending on the regimen used.

Multicolor flow cytometry: sampling of bone marrow MNCs is preferred over peripheral blood samples; this requires at least 1 × 10^6 MNCs for analysis (about 2 mL of bone marrow or 5–10 mL of peripheral blood provides a sufficient number of cells for multiple analysis).

RQ-PCR: sampling of bone marrow MNCs is preferred; this requires at least 1 × 10^7 MNCs for initial marker characterization and generation of individual dilution series; 1 × 10^5 MNCs are sufficient for follow-up analysis.

The minimal limit of assay sensitivity (to declare MRD negativity) should be <1 × 10^-4 (<0.01%).

High-sensitivity PCR assays (for analysis of Ig or TCR gene rearrangements) require the identification of patient-specific markers that involve direct sequencing, and may therefore be labor- and resource-intensive for routine application in the clinical practice setting.

Recommendations on the minimal technical requirements for MRD assessment (both for PCR and flow cytometry methods) and definitions for response based on MRD results (e.g., MRD negativity, non-quantifiable MRD positivity, quantifiable MRD positivity) have recently been published as a result of a consensus development meeting held by ALL study groups across Europe. The recommendations were made in an effort to standardize MRD measurements and MRD data reporting within the context of clinical trials.

MRD evaluations should be performed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories with expertise in MRD assays; note that results from one lab to another may not be directly equivalent or comparable.

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, including neurofibromatosis, Klinefelter syndrome, Fanconi anemia, Shwachman syndrome, Bloom syndrome, and ataxia telangiectasia.

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 risk-adapted therapy, and the advent of new targeted agents. Data from the SEER database have shown a 5-year overall survival (OS) of 86% to 89% for children; however, AYA patients were reported to have a 5-year OS between 42% to 63%, depending on the age range. Adults have the poorest 5-year OS rate: 24.1% for patients between the ages of 40 and 59 and an even lower rate of 17.7% for patients between the ages of 60 and 69.

Although the exact OS percentage can vary based on how the age range is defined for pediatric, AYA, and adult patients, the trend is nonetheless clear that OS decreases substantially with increased age. The exception is infants younger than age 1, which is an age group that has not seen any improvement in survival over the past 30 years. The 5-year OS in this population is 55.8% (see “Cytogenetic and Molecular Subtypes,” page 1260). Cure rates for AYA patients with ALL remain suboptimal compared with those for children, although substantial improvements have been seen with the recent 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-RUNX1 ALL and hyperploidy, occur less frequently among AYA patients compared with children, whereas the incidence of ALL with BCR-ABL (Ph-positive ALL) is higher in AYA patients.

Diagnosis

Clinical Presentation and Diagnosis

The clinical presentation of ALL is typically non-specific and may include fatigue or lethargy, constitutional symptoms (eg, fevers, night sweats, weight loss), dyspnea, dizziness, infections, and easy bruising or bleeding. Among children, pain in the extremities or joints may be the only presenting symptom. The presence of lymphadenopathy, splenomegaly, and/or hepatomegaly on physical examination may be found in approximately 20% of patients. Abdominal masses from gastrointestinal involvement or chin numbness from cranial nerve involvement are more suggestive of mature B-cell ALL.

The diagnosis of ALL generally requires demonstration of 20% or greater bone marrow lymphoblasts on hematopathology review of bone marrow aspirate and biopsy materials (see ALL-1, page 1242). The 2008 WHO classification lists ALL and lymphoblastic lymphoma as the same entity, distinguished only by the primary location of the disease. When the disease is restricted to a mass lesion primarily involving nodal or extranodal sites with no or minimal involvement in blood or bone marrow (generally defined as <20% lymphoblasts in the marrow), the case would be consistent with a diagnosis of lymphoblastic lymphoma.

Lymphoblastic lymphoma was previous categorized with non-Hodgkin lymphomas and is associated with exposure to radiation or pesticide and congenital or acquired immunosuppression. However, based on morphologic, genetic, and immunophenotypic features, lymphoblastic lymphoma is indistinguishable from ALL.

Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens. Chemotherapy should be initiated as soon as possible; combination chemotherapy has shown improved response though relapse is common. Studies show a 5-year disease-free survival (DFS) rate between 60% and 80% in children and between 55% and 95% in adults after a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other CHOP-like regimens. Hyper-CVAD (cycles of fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with cycles of high-dose methotrexate and cytarabine) is also a common regimen used for lymphoblastic lymphoma. A response rate of 100% was seen in a singular study, with 91% of patients experiencing a complete response (CR) and a 3-year progression-free survival (PFS) of 66%. However, it should be noted that 40% to 60% of adults experience relapse, suggesting that other treatments, including hematopoietic cell transplantation (HCT), may be warranted.
Hematopathology evaluations should include morphologic examination of malignant lymphocytes using Wright-Giemsa–stained slides and hematoxylin and eosin–stained core biopsy and clot sections; comprehensive immunophenotyping with flow cytometry (see “Immunophenotyping”, below); and assessment of cytogenetic or molecular abnormalities. Identification of specific recurrent genetic abnormalities is critical for disease evaluation, optimal risk stratification, and treatment planning (see “Cytogenetic and Molecular Subtypes,” page 1260). Subtypes of B-cell ALL with recurrent genetic abnormalities include the following: hyperdiploidy (DNA index >1.16; 51–65 chromosomes); hypodiploidy (<44 chromosomes); t(9;22)(q34;q11.2), BCR-ABL1; t(v;11q23), MLL rearrangement; t(12;21)(p13;q22), ETV6-RUNX1; t(1;19)(q23;p13.3), TCF3-PBX1; and t(5;14)(q31;q32), IL3-IGH.28 Presence of recurrent genetic abnormalities should be evaluated using karyotyping of G-banded metaphase chromosomes (conventional cytogenetics) and/or through interphase fluorescence in situ hybridization (FISH) assays that include probes capable of detecting the genetic abnormalities.

Immunophenotyping

Immunophenotypic classification of ALL involves flow cytometry to determine the presence of cell surface antigens on lymphocytes. ALL can be broadly classified into 3 groups based on immunophenotype, which include precursor B-cell ALL, mature B-cell ALL, and T-cell ALL (see ALL-A, page 1249). Among children, B-cell lineal ALL constitutes approximately 88% of cases;30 in adult patients, subtypes of B-cell lineage ALL represent approximately 75% of cases (including mature B-cell ALL that constitutes 5% of adult ALL), whereas the remaining 25% comprise T-cell lineage ALL.30 Within the B-cell lineage, the profile of cell surface markers differs according to the stage of B-cell maturation, which include early precursor B-cell (early pre-B-cell), pre-B-cell, and mature B-cell ALL. Early pre-B-cell ALL is characterized by the presence of terminal deoxynucleotidyl transferase (TdT), the expression of CD19/CD22/CD79a, and the absence of CD10 (formerly termed common ALL antigen) or surface immunoglobulins. Pre-B-cell ALL is characterized by the presence of cytoplasmic immunoglobulins and CD10/CD19/CD22/CD79a expression123,24,31 and was previously termed common B-cell ALL due to the expression of CD10 at diagnosis. Mature B-cell ALL shows positivity for surface immunoglobulins and clonal lambda or kappa light chains, and is negative for TdT.1 CD20 may be expressed in approximately 50% of B-cell lineage ALL in adults, with a higher frequency (>80%) observed in cases of mature B-cell ALL.32,33

T-cell lineage ALL is typically associated with the presence of cytoplasmic CD3 (T-cell lineage blasts) or cell surface CD3 (mature T cells) in addition to variable expression of CD1a/CD2/CD5/CD7 and expression of TdT.1,23,25 CD52 may be expressed in 30% to 50% of T-cell lineage ALL in adults.1 Combined data from the GMALL 06/99 study and the GMALL 07/03 study revealed a distribution of T-cell lineage ALL among 3 subgroups: cortical/thymic (56%), medullary/mature (21%), and early (23%) T-cell ALL.20 The latter is further divided between early T-cell precursor (ETP) ALL and early immature T-ALL. Early immature T-ALL includes both pro-T-ALL and pre-T-ALL immunophenotypes (for specific markers, see ALL-A, page 1249).

ETP ALL represents a distinct biologic subtype of T-cell lineage ALL that accounts for 12% of pediatric T-ALLs (and about 2% of ALL) and is associated with poor clinical outcomes even with contemporary treatment regimens. This subtype is characterized by the absence of CD1a/CD8, weak expression of CD5 (<75% positive lymphoblasts), and the presence of 1 or more myeloid or stem cell markers (CD117, CD34, HLA-DR, CD13, CD33, CD11b, or CD65) on at least 25% of lymphoblasts.34 In a study of 239 patients with T-ALL, gene expression profiling, flow cytometry, and single nucleotide polymorphism array analysis were employed to identify patients with ETP-ALL.34 ETP-ALL was associated with a 10-year OS of 19% (95% CI, 0%–92%) compared with 84% (95% CI, 72%–96%) in the patients with non-ETP ALL. The 10-year event-free survival (EFS) was similarly poor in patients with ETP-ALL (22%; 95% CI, 5%–49%) compared with patients with non-ETP ALL (69%; 95% CI, 53%–84%). Remission failure and hematologic relapse were significantly higher for patients with ETP-ALL (P<.0001).34 A pivotal study from Zhang et al35 identified a high frequency of activating mutations in the cytokine receptor and RAS signaling pathways that included NRAS, KRAS, FLT3, IL7R, JAK3, JAK1, SH2B3, and BRAF. Furthermore, inactivating mutations of genes that en-
Cytogenetic and Molecular Subtypes

Recurrent chromosomal and molecular abnormalities characterize ALL subtypes in both adults and children (Table 1) and often provide prognostic information that may weigh into risk stratification and treatment decisions. The frequency of certain subtypes differs between adult and childhood ALL, which partially explains the difference in clinical outcomes among patient populations. Among children with ALL, the most common chromosomal abnormality is hyperdiploidy (>50 chromosomes; 25% of cases) seen in B-cell lineage ALL compared with 7% in the adult ALL patient population. The ETV6-RUNX1 subtype (also within the B-cell lineage) is among the most commonly occurring subtypes (22%) in childhood ALL compared with adults (2%). Both hyperdiploidy and ETV6-RUNX1 subtypes are associated with favorable outcomes in ALL. Ph-positive ALL, associated with poor prognosis, is relatively uncommon in childhood ALL (3%), whereas this abnormality is the most common subtype among adults (25%). The frequency of Ph-positive ALL increases with age (10%, patients 15–39 years; 25%, patients 40–49 years; 20%–40%, patients >50 years of age). Moreover, younger children (1–9 years of age) with Ph-positive ALL have a better prognosis than adolescents with this subtype.

Philadelphia-like (Ph-like) ALL is a subgroup of B-cell lineage ALL associated with unfavorable prognosis. Similar to Ph-positive ALL, the 5-year DFS in this population is estimated to be 60%, however, this genotype is 4 to 5 times more frequent.

Table 1 Common Chromosomal and Molecular Abnormalities in Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>Gene</th>
<th>Frequency in Adults</th>
<th>Frequency in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdiploidy (&gt;50 chromosomes)</td>
<td>--</td>
<td>7%</td>
<td>25%</td>
</tr>
<tr>
<td>Hypodiploidy (&lt;44 chromosomes)</td>
<td>--</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Philadelphia chromosome (Ph)</td>
<td>BCR-ABL1</td>
<td>25%</td>
<td>2%–4%</td>
</tr>
<tr>
<td>t(12;21)(p13;q22)</td>
<td>ETV6-RUNX1 (TEL-AML1) MLL</td>
<td>2%</td>
<td>22%</td>
</tr>
<tr>
<td>t(v;11q23) [eg, t(4;11), t(9;11)], t(11;19)</td>
<td>TCF3-PBX1 (E2A-PBX1) IIL3-IGH</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>t(1;19)(q23;p13)</td>
<td>c-MYC</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>t(5;14)(q31;q32)</td>
<td>TAL-1a</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>t(8;14), t(2;8), t(8;22)</td>
<td>HOX11 (TLX1)a</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>t(10;14)(q24;q11)</td>
<td>HOX11L2b</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>t(5;14)(q35;q32)</td>
<td>TCRα and TCRβ</td>
<td>20%–25%</td>
<td>10%–20%</td>
</tr>
<tr>
<td>t(11;14)(q11) [eg, (p13;q11), (p15;q11)]</td>
<td>BCR-ABL1-like</td>
<td>variousb</td>
<td>10%–30%</td>
</tr>
<tr>
<td>Ikaros</td>
<td>IKZF1</td>
<td>50%</td>
<td>12%–17%</td>
</tr>
</tbody>
</table>

*Abnormalities observed exclusively in T-cell lineage ALL; all others occur exclusively or predominantly in B-cell lineage ALL.
aSee text for more details.

Hematologic malignancies related to ALL include acute leukemias with ambiguous lineage, such as the mixed phenotype acute leukemias (MPAL). MPAL include bilineage leukemias, in which 2 distinct populations of lymphoblasts are identified, with 1 meeting the criteria for acute myeloid leukemia. Another type of MPAL is the biphenotypic type, in which a single population of lymphoblasts expresses markers consistent with B-cell or T-cell ALL, in addition to expressing myeloid or monocytic markers. Notably, myeloid-associated markers such as CD13 and CD33 may be expressed in ALL, and the presence of these markers does not exclude this diagnosis. The identification of mixed lineage leukemias should follow the criteria presented in the 2008 WHO classification of neoplasms. The initial immunophenotyping panel should be sufficiently comprehensive to establish a leukemia-associated phenotype that may include expression of nonlineage antigens; these are useful in classification, particularly for MPAL.

The identification of mixed lineage leukemias is among the most commonly occurring subtypes (22%) in childhood ALL compared with adults (2%). Both hyperdiploidy and ETV6-RUNX1 subtypes are associated with favorable outcomes in ALL. Ph-positive ALL, associated with poor prognosis, is relatively uncommon in childhood ALL (3%), whereas this abnormality is the most common subtype among adults (25%). The frequency of Ph-positive ALL increases with age (10%, patients 15–39 years; 25%, patients 40–49 years; 20%–40%, patients >50 years of age). Moreover, younger children (1–9 years of age) with Ph-positive ALL have a better prognosis than adolescents with this subtype.

Philadelphia-like (Ph-like) ALL is a subgroup of B-cell lineage ALL associated with unfavorable prognosis. Similar to Ph-positive ALL, the 5-year DFS in this population is estimated to be 60%, however, this genotype is 4 to 5 times more frequent.
in children and young adults than the Ph-positive ALL phenotype. Although this subgroup is Ph-negative, there is an otherwise similar genetic profile to the Ph-positive ALL subgroup including mutation of the \( \text{IKZF1} \) gene. Genomically, this subtype is further identified by mutations in the Ras and JAK/STAT5 pathways as the common mechanism of transformation. These include mutations in the \( \text{ABL1}, \text{EPOR}, \text{JAK2}, \text{PDGFR}\beta, \text{EBF1}, \text{FLT2}, \text{IL7R}, \) and \( \text{SH2B3} \) genes.\(^{45-46} \) A recent publication found kinase-activating alternations in 91% of Ph-like ALL cases.\(^{37} \)

Therefore, use of the \( \text{ABL1} \) tyrosine kinase inhibitor (TKI) imatinib or other targeted therapies may significantly improve patient outcomes in this subgroup.

Other cytogenetic and molecular subtypes are associated with ALL and prognosis. Although not as common, translocations in the \( \text{MLL} \) gene (in particular, cases with \( t(4;11) \) translocation) are known to have poor prognosis.\(^{22,32} \) Hypodiploidy is associated with poor prognosis and is seen in 1% to 2% of patients.\(^{22,48} \) Low hypodiploidy (30–39 chromosomes)/near triploidy (60–68 chromosomes) and complex karyotype (≥5 chromosome abnormalities) are also associated with poor prognosis and occur more frequently with increasing age (1%–3%, patients 15–29 years; 3%–6%, patients 30–59 years; 5%–11%, patients >60 years of age).\(^{38} \)

In B-cell ALL, mutations in the Ikaros gene (\( \text{IKZF1} \)) are associated with a poor prognosis and a greater incidence of relapse. \( \text{IKZF1} \) mutations are seen in approximately 15% to 20% of pediatric B-cell ALL\(^{95,50} \) and at a higher frequency of more than 75% in patients who are also \( \text{BCR-ABL} \) positive.\(^{45,50} \) Incidence in adults is about 50% in B-cell ALL\(^{31,52} \) and about 65% when also \( \text{BCR-ABL} \) positive.\(^{33,54} \) A study evaluating the relationship between \( \text{BCR-ABL1} \)-like and \( \text{IKZF1} \) in children with B-cell precursor ALL showed that 40% of cases had co-occurrence of these mutations.\(^{55} \) The presence of either mutation was indicative of poor prognosis and was independent of conventional risk factors. Both mutations are considered strong independent risk factors for B-cell ALL and are applicable across a broad range of stratified ALL including patients with intermediate MRD. The DCOG ALL-11 trial will incorporate \( \text{IKZF1} \) as a risk factor, and patients will receive an additional year of maintenance therapy if \( \text{IKZF1} \) is detected. However, despite the prognostic value and potential for risk stratification based on the presence of \( \text{IKZF1} \) mutations, there are no suitable testing methods for these mutations, thereby limiting current clinical applications.

**Management of Relapsed ALL**

**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 have reported a median OS of only 4.5 months to 6 months, and a 5-year OS rate of 3% to 10% among patients who experience relapse after initial treatment.\(^{56-59} \) 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 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%; \( P < .001 \)).\(^{57} \) 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 experienced relapse within 2 years (11% vs 5%; \( P < .001 \)).\(^{58} \) In the preimatinib era, patients with Ph-positive ALL who had relapse 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% to 6% among patients subsequently treated for relapsed Ph-positive ALL\(^{56,58} \).

The incorporation of TKIs such as imatinib in the frontline treatment regimen for Ph-positive ALL has become the established standard of care. However, the emergence of resistance to TKI therapy poses a challenge for patients with disease that is primarily refractory to or that relapses after initial treatment with TKI-containing regimens. Point mutations within the \( \text{ABL} \) kinase domain and alternative signaling pathways mediated by the SRC family kinase have been implicated as mechanisms of resistance to imatinib.\(^{60-65} \) Mutations within the \( \text{ABL} \) kinase domain have been identified in a large proportion of patients who experience disease recurrence after imatinib-containing therapy.\(^{51,63} \) Moreover, \( \text{ABL} \)
kinase domain mutations may be present in a small group of imatinib-naive patients even before initiation of any TKI therapy. 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. Both TKIs have been evaluated as single-agent therapy in patients with Ph-positive ALL that is resistant or intolerant to imatinib treatment. 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 (n = 84) resistant to imatinib; the once-daily dosing resulted in higher response rates (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 PFS was longer (4 vs 3 months). These differences in outcomes between the dosing arms were not statistically significant. Dasatinib is currently approved in the United States for the treatment of patients with Ph-positive ALL that is intolerant or resistant to prior therapy.

Dasatinib in combination with hyperCVAD was investigated in a phase II trial (n = 34) including patients with Ph-positive relapsed ALL (n = 19) and patients with lymphoid blast phase chronic myelogenous leukemia (CML; n = 15). An overall response rate of 91% was obtained with 26 patients experiencing complete cytogenetic remission, 13 patients having complete molecular response, and 11 patients having a major molecular response. In the study, 9 patients went on to receive allogeneic HCT, including 2 patients with ALL. In the patients with relapsed ALL, 30% remained in CR at 3 years (median, 8.8 months) with a 3-year OS of 26% (median, 9 months). At the median follow-up of 52 months (range, 45–59), 2 patients with ALL were still alive (11%).

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. 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.

Ponatinib is another TKI that was initially approved by the US FDA (December 2012) for the treatment of adult patients with chronic, accelerated, or blast phase Ph-positive CML or Ph-positive ALL, with resistance or intolerance to prior therapy. Though it was temporarily removed from the market in November 2013, ponatinib distribution resumed in December 2013 after revision of both the prescribing information and a REMS 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. In a phase I dose-escalation study that evaluated ponatinib in heavily pretreated patients with Ph-positive leukemias resistant to prior TKI agents, major hematologic response was reported in 36% of the subgroup of patients with accelerated or blast phase CML or Ph-positive ALL (n = 22). Major cytogenetic response occurred in 7 patients (32%), with a complete cytogenetic response in 3 patients (14%). Response outcomes in the small group of patients with T315I mutation (n = 7) appeared similar to those in the overall subgroup.

In a multicenter, open-label, phase II study (PACE trial; n = 449 enrolled; median age, 59 years; range, 18–94 years), ponatinib showed substantial activity in patients with Ph-positive leukemias resistant or intolerant to second-generation TKIs. Patients in this trial were heavily pretreated, with 58% having previously received at least 3 TKI agents. Among the subgroup of patients with Ph-positive ALL (n = 32), the median age was 62 years (range, 20–80 years) and 41% were age 65 years or older. Major hematologic response among the subgroup with Ph-positive ALL was 41%; major and complete cytogenetic response was 47% and 38%, respectively. The estimated PFS rate at 12 months was 7% (median, 3 months), and the OS rate at 12 months was estimated to be 40% (median, 8 months). In the subset of patients with Ph-positive ALL with ABL T315I mutation (n = 22), major hematologic response was 36%, and major and complete cytogenetic response was 41% and 32%, respectively. No significant differences in duration or OS outcomes were apparent based on ABL T315I mutation status; however, the patient...
numbers were small. The most common overall treatment-related adverse events in the PACE trial included thrombocytopenia (37%), rash (34%), dry skin (32%), abdominal pain (22%), neutropenia (19%), and anemia (13%); pancreatitis was the most common serious event, reported in 5% of patients. These studies demonstrated the activity of ponatinib in patients with Ph-positive leukemias resistant to other TKIs, including those with Ph-positive ALL harboring a T315I mutation.

Bosutinib, a TKI that acts as a dual inhibitor of BCR-ABL and SRC family kinases, was approved (September 2012) by the FDA for the treatment of chronic, accelerated, or blast phase Ph-positive CML in adult patients with resistance or intolerance to prior therapy. The FDA approval was based on an open-label, multicenter phase I/II trial in patients with chronic, accelerated, or blast phase CML previously treated with at least one prior TKI therapy; all patients had received prior imatinib therapy. The efficacy and safety of this agent in patients with relapsed/refractory Ph-positive ALL have not been established.

Treatment options are extremely limited for patients with Ph-positive ALL who experience relapse after receiving allogeneic HCT. Several published cases have reported on the feasibility of inducing a molecular CR with dasatinib in patients with Ph-positive ALL who have experienced an early relapse after first allogeneic HCT. The patients subsequently received a second allogeneic HCT. Studies entailing donor lymphocyte infusion (DLI) to induce further graft-versus-leukemia effect in patients with Ph-positive ALL experiencing disease relapse after allogeneic HCT have reported little to no benefit, though it has been suggested that this is due to a leukemic burden that may have been too high to control effectively. 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 polymerase chain reaction [PCR]) after allogeneic HCT may eliminate residual leukemic clones and thereby prevent overt hematologic relapse. Moreover, case reports have suggested using newer TKIs, such as dasatinib and nilotinib, along with DLI to manage relapse after allogeneic HCT. A case report described the treatment course and outcome in a patient who experienced early hematologic relapse after allogeneic HCT (performed in first CR). The patient responded to imatinib-based multiagent chemotherapy and DLI (with persistent residual disease based on BCR-ABL transcripts) but then experienced a second hematologic relapse. The disease progressed through second-line therapy with imatinib-based multiagent chemotherapy, and the patient received dasatinib, which resulted in a complete hematologic response; the patient subsequently underwent a second allogeneic HCT and maintained a molecular CR lasting 18 months. Although these approaches are promising, only limited data based on case reports are available. Evidence from prospective studies is needed to establish the role of DLI, with or without TKIs, in the treatment of relapse.

Currently, bone marrow transplantation is the only cure for relapsed/refractory ALL, but many patients are not eligible for transplant based on age or progression of the disease. The pretreatment of patients with chimeric antigen receptor (CAR) T cells has served as a bridge for transplant, and patients who were formally unable to undergo transplantation due to poor remission status have a CR and ultimately transplantation. This treatment is associated with fewer side effects compared with the current standard-of-care regimens; although side effects from CAR T cells may be severe, they have been reversible. Adverse events are attributed to cytokine release syndrome and macrophage activation that occurs in direct response to adoptive cell transplant resulting in high fever, hypotension, breathing difficulties, delirium, aphasia, and neurologic complications. Improvement in patient monitoring has shown successful treatment of these symptoms with the monoclonal antibody tocilizumab, an antagonist of interleukin-6. Based on their ability to elicit a significant response towards elimination of tumor cells, multicenter phase II studies are planned for CAR T cells in the treatment of relapsed/refractory ALL.

**NCCN Recommendations for Ph-Positive ALL**

**Patients with Relapsed/Refractory Ph-Positive ALL:** Mutation testing for the ABL gene should be considered in patients with Ph-positive ALL that has relapsed after or is refractory to initial TKI-containing therapy given that certain mutations may account for the observed resistance to induction therapy (see ALL-7, page 1248). The panel has largely adopted the recommendations for treatment options...
based on ABL mutation status for CML, as published by the European LeukemiaNet.98 Based on these published recommendations, dasatinib (if not administered during initial induction) could be considered for patients with relapsed/refractory Ph-positive disease that have the mutations Y253H, E255K/V, or F359V/C/I. For patients with relapsed/refractory disease that have the mutations V299L, T315A, or F317L/V/I/C, nilotinib could be considered. The TKI bosutinib has been added for patients with the mutations E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H. Ponatinib has activity against and is effective in treating the T315I mutation. However, due to the high frequency of serious vascular events, the FDA indication is restricted to the treatment of patients with the T315I mutation or in patients with disease resistant to other TKI therapies. For all other mutations of the ABL gene, high-dose imatinib, dasatinib, or nilotinib may be considered.

For patients with relapsed/refractory disease, participation in a clinical trial is preferred. In the absence of an appropriate trial, patients may be considered for second-line therapy with an alternative TKI (ie, different from the TKI used as part of induction therapy) alone, TKI combined with multiagent chemotherapy, TKI combined with corticosteroids (especially for elderly patients who may not tolerate multiagent combination therapy), or allogeneic HCT if a donor is available. For patients with disease that relapses after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or DLI. Blinatumomab may be considered for patients with Ph-positive precursor B-cell ALL that is refractory to TKIs (see ALL-D 3 of 4, page 1254).

**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.97–99 Among those who experience relapse, only approximately 30% experience long-term remission with subsequent therapies.100–102 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%.97 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%, and 43.5%, respectively (P < .0001). Intermediate relapse was defined as relapses occurring between 18 and 36 months from diagnosis; late cases were defined as relapses occurring 36 months or more from diagnosis. For cases of isolated central nervous system (CNS) relapse, the 5-year survival estimates among early (n = 175), intermediate (n = 180), and late (n = 54) relapsing disease were 43.5%, 68%, and 78%, respectively (P < .0001).97 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.97 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: age 1 to <10 years of age and white blood cell [WBC] count <50 X 10⁹/L).103 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) compared with late bone marrow relapse.103 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) compared with late extramedullary relapse. In a multivariate regression analysis, early bone marrow and extramedullary relapse were independent predictors of poorer EFS outcomes.103

AYA and adult patients with ALL who experience relapse after initial therapy have extremely poor long-term outcomes. Based on data from patients with disease relapse after frontline therapy in the MRC UKALL XII/ECOG E2993 study and PETHHEMA studies, the median OS after relapse was only 4 to 6 months; the 5-year OS rate was 7% to 10%.36,57 Approximately 20% to 30% of patients experience a second CR with second-line therapies.57,59 Factors predictive of more favorable outcomes after subsequent therapies included younger age and a first CR duration of more than 2 years.57,104 Among younger patients (age <30 years) whose disease relapsed after experiencing a first CR duration longer than 2 years with frontline treatment in PETHHEMA trials, the 5-year OS rate from the time of first relapse was 38%.57
The treatment of AYA and adult patients with relapsed and/or refractory ALL remains a challenge. 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 relapsed or refractory ALL (n = 61; median age, 12 years; range, 1–20 years; median 3 prior regimens), the response rate (CR plus CR without platelet recovery [CRp]) was 20%. Among the patients with responding disease, the median duration of remission was 29 weeks. Although the median OS for all patients was only 13 weeks, the median OS for patients with a CR had not yet been reached at the time of publication; median OS was 54 weeks for patients with a CRp and 30 weeks for patients with a partial remission. Single-agent clofarabine in the relapsed/refractory setting has been associated with severe liver toxicities (generally reversible) and frequent febrile episodes including grade 3 or 4 infections and febrile neutropenia.

In a small phase II study evaluating the combination of clofarabine with cyclophosphamide and etoposide in pediatric patients with refractory or multiple relapsed ALL (n = 25; median age, 12.5 years), the regimen resulted in a CR rate of 52% (plus an additional 4% CRp), with an 18-month OS probability of 39% among responders. In subsequent, small phase II studies in pediatric patients (age 1–21 years) with relapsed/refractory ALL, this combination induced response rates (CR plus CRp) of 42% to 44%. A multicenter retrospective study of data from pediatric patients treated with clofarabine outside of the clinical trial setting (n = 23; age 0–17 years) reported that among those treated with the combination of clofarabine, cyclophosphamide, and etoposide (n = 18), the CR rate was 56%. The combination regimen of clofarabine, cyclophosphamide, and etoposide has been associated with prolonged and severe myelosuppression, febrile episodes or severe infections (including sepsis or septic shock), mucositis, and liver toxicities including fatal venoocclusive disease (the latter occurring in the postallogeneic HCT setting). Moreover, data are very limited with this combination regimen in adult patients with ALL. Because the use of this regimen requires close monitoring and intensive supportive care measures, patients should only be treated in centers with expertise in the management of ALL.

Clofarabine has also been shown to be active in combination with other chemotherapy regimens in adults with relapsed/refractory disease. In a study from GRAALL, clofarabine in combination with conventional chemotherapy (cyclophosphamide, or a more intensive regimen with dexamethasone, mitoxantrone, etoposide, and asparaginase) yielded a CR rate of 44% in patients with relapsed/refractory ALL (n = 55); the median OS was 6.5 months after a short median follow-up of 6 months. The most common grade 3 or 4 toxicities included infection (58%) and liver toxicities (24%). Another regimen for advanced disease, comprising ifosfamide, etoposide, and mitoxantrone, was evaluated in a small phase II study in adult patients with relapsed or refractory ALL (n = 11); 8 patients (73%) experienced a CR, and the median DFS and OS durations from time of remission were 3.1 and 7.7 months, respectively. The combination of high-dose cytarabine and idarubicin was evaluated as a regimen in adult patients with relapsed/refractory ALL (n = 29). In this study, 11 patients (38%) experienced a CR, and the median OS for responding patients was 8 months. Four patients who experienced a CR with this therapy proceeded to allogeneic HCT. The median OS for all patients on the study was 6 months.

A phase II study from MD Anderson Cancer Center evaluated an augmented hyper-CVAD regimen (that incorporated asparaginase, intensified vincristine, and intensified dexamethasone) as therapy in adults with relapsed/refractory ALL (n = 90; median age, 34 years; range, 14–70 years; median 1 prior regimen). 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 was lower among the subgroup who received pegaspargase than those who received L-asparaginase (1% vs 12%). 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. 

Nelarabine is a nucleoside analog that is currently approved for the treatment of patients with T-cell ALL who have not experienced disease response to or who have relapsed disease after at least 2 chemo-
therapy regimens.116 A phase II study of nelarabine monotherapy in children and adolescents with relapsed/refractory T-cell ALL or T-cell non-Hodgkin’s lymphoma (n = 121) showed a 55% response rate among the subgroup with T-cell 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).100 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 relapsed/refractory T-cell 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-cell ALL, n = 26).117 The CR rate (including CR with incomplete blood count recovery [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 1 case of grade 4 CNS toxicity (reversible) was observed.117

Vincristine remains an important part of the backbone of chemotherapy agents used in ALL treatment. Vinca alkaloids are known to be associated with neurologic toxicities, generally limiting their use at higher doses. 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.118,119 VSLI was recently 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).120 Approximately 50% of patients had received 3 or more prior lines of therapy. In addition 48% of patients had undergone prior HCT, and all patients had previously been treated with a regimen containing standard vincristine. The CR (CR + CRi) rate with single-agent VSLI was 20%. The median duration of CR was 23 weeks (range, 5–66 weeks) and median OS for all patients was 20 weeks (range, 2–94 weeks); median OS for patients achieving a CR was 7.7 months.120 The incidence of early induction death (30-day mortality rate) was 12%.120 These outcomes appeared favorable compared with published 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%).120,121 The most common grade 3 or greater treatment-related toxicities with VSLI included neuropathy (23%), neutropenia (15%), thrombocytopenia (6%), anemia (5%; no grade 4), and tumor lysis syndrome (5%). Febrile neutropenia occurred in 3% of patients (no grade 4).120 Based on data from the RALLY study, VSLI was approved (in September 2012) by the FDA for the treatment of adult patients with Ph-negative ALL in second or greater relapse or whose disease progressed after 2 or more therapies.122

In December 2014, the FDA approved blinatumomab for the treatment of relapsed or refractory Ph-negative precursor B-cell ALL. Blinatumomab is a bispecific anti-CD3/CD19 monoclonal antibody that showed high CR rates (67%; including rapid MRD-negative responses) in patients with relapsed/refractory B-precursor ALL (n = 18).123 In an earlier phase II study, blinatumomab was shown to eliminate residual disease in 80% of patients with relapsed or MRD-positive B-precursor ALL after intensive chemotherapy (N = 21; n = 20 evaluable).124 After a median follow-up of 33 months, the hematologic relapse-free survival (RFS) rate was 61%. This study enrolled 5 patients with Ph-positive B-cell precursor ALL, of which 3 patients responded within the first 2 cycles of treatment. While there were not enough patients for definitive analysis of this subgroup, data suggest that blinatumomab may also improve outcomes for relapsed or refractory Ph-positive precursor B-cell ALL.

FDA approval of blinatumomab followed the release of data from a large phase II confirmatory study of 189 patients with Ph-negative relapsed or refractory B-cell ALL that demonstrated a CR or CRp in 43% of patients within the first 2 cycles of treatment.125 The Alcantara trial is currently investigating blinatumomab in a larger cohort of patients with Ph-positive B-cell ALL with relapsed disease or disease refractory to at least one second-generation TKI (dasatinib, nilotinib, bosutinib, ponatinib) or intolerant to second generation TKI and intolerant or refractory to imatinib mesylate (clinicaltrials.gov; NCT02000427). Although data from this study are not yet available, blinatumomab is considered by the panel as a possible treatment option for Ph-positive ALL.
precursor B-cell ALL refractory to TKIs based on the lack of other treatment alternatives.

Blinatumomab is a component of the growing arsenal of immunotherapies for the treatment of cancer. Data demonstrate a profound improvement in the treatment of patients with relapsed/refractory ALL, a population that has a historically poor prognosis and limited treatment options; however, there are significant and unique side effects to this treatment compared to the current standard-of-care regimens. Cytokine release syndrome is a serious adverse event with peak cytokine levels in the first 2 days after initiation of blinatumomab infusion. Symptoms of cytokine release syndrome include pyrexia, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, and increased total bilirubin. Neurologic toxicities have been reported in 50% of patients (median onset, 7 days). Grade 3 or higher neurologic toxicities have occurred in 15% of patients. Serious risks may occur with preparation or administration errors. The incidence of adverse events can be reduced with patient monitoring for early intervention at the 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.

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 graft-versus-host disease. To circumvent this issue, current advances are focused on the use of the patient’s own T cells to target the tumor. The generation of CAR T cells to treat ALL is a significant advancement in the field. Briefly, T cells from the patient are harvested and engineered with a receptor that targets a cell surface tumor-specific antigen (e.g., 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 a significant advantage and avoids the issue of tumor evasion of the immune system via receptor down regulation. The viral vector in CAR T cells causes T cell expansion and proliferation following antigen recognition, and once modified, CAR T cells can be expanded ex vivo for approximately 2 weeks to produce high numbers before intravenous infusion back into the patient. After infusion, debulking of tumors occurs in less than a week, though these cells may remain in the body for extended periods of time to provide immunosurveillance against relapse.

Clinical trials in patients with relapsed/refractory ALL have shown promising results. There are several trials using CAR T cells that differ in the receptor construct. One trial involving the modified receptor termed 19-28z, found an overall CR in 14 of 16 patients with relapsed or refractory B-cell ALL after infusion with CAR T cells. This average remission rate of 88% is significantly improved compared with the average remission rate for patients receiving standard-of-care chemotherapy after relapse (approximately 30%). Furthermore, 7 of 16 patients were able to receive an allogeneic HCT, suggesting that CAR T cells may provide a bridge to allogeneic HCT. No relapse has been seen in patients that had allogeneic HCT (followup, 2–24 months); however 2 deaths occurred from transplant complications. In a recent abstract, followup data of adult patients enrolled on this trial (n = 24, 22 evaluable) showed a 91% CR rate after the infusion and 18 of 20 patients achieved an MRD-negative CR. Of the 13 patients that were transplant eligible, 10 underwent allogeneic HCT. The median followup was 7.4 months and a durable response was indicated by 6 patients remaining disease-free past 1 year. The median OS is 9 months.

A second receptor construct that is defined by the alteration in the single chain variable fragment of CD19 (anti-CD19 scFv/4-1BB/CD3ζ) has shown similar results to the 19-28z CAR T cells in terms of overall CR. These cells, more simply referred to as CTL019, were infused into 16 children and 4 adults with relapsed/refractory ALL; a CR following therapy was achieved in 14 patients. Of these 20 patients, there was no response of the disease to treatment in 3 patients and disease response to therapy for an additional 3 patients was still under evaluation. A followup study of 25 children and 5 adults showed a morphologic CR of 90% (27 of 30) patients within a month of treatment and an OS of 78% (95% CI, 65–95) and EFS of 78% (95% CI, 51–88) at 6 months. There were 19 patients in sustained remission, of whom 15 received no further therapy.

Another novel monoclonal antibody currently under clinical investigation is inotuzumab ozogami-
The study showed that...102 An ongoing phase III study to evaluate the efficacy and safety of InO compared to standard of care consisting of intensive chemotherapy, has demonstrated higher CR/CRi (InO, 80.7% vs standard of care, 33.3%; \( P < .0001 \)), duration of remission (InO, 4.6 vs standard of care, 3.1 months; \( P = .0169 \)) and MRD-negative rates (78.4% vs 28.1%; \( P < .0001 \)). Similar to previous studies, InO had a higher rate of liver toxicities (9% vs 3%) and veno-occlusive liver disease (InO, 15 patients vs standard of care, 1 patient). Although study data are promising, InO is currently investigational and is not FDA-approved for any indication.

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.138 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, such as T-cell ALL.101,102,139 In a retrospective analysis involving children and adolescents (age 1–18 years) with pre-B-cell ALL experiencing a second CR after bone marrow relapse, outcomes were compared between patients who underwent allogeneic HCT (\( n = 186 \)) and those who received chemotherapy regimens in the POG trials (\( n = 188 \)).139 The study showed that among patients with early bone marrow relapse (<36 months from time of diagnosis), total body irradiation (TBI)–containing allogeneic HCT was associated with significantly lower risks of a second relapse (relative risk, 0.49; 95% CI, 0.33–0.71; \( P < .001 \)) or overall mortality (relative risk, 0.58; 95% CI, 0.41–0.83; \( P = .003 \)) compared with chemotherapy regimens. This advantage with TBI-containing allogeneic HCT was not seen among the subgroup with a late first relapse (≥36 months), and no advantages were seen with the use of non–TBI-containing HCT regimens regardless of the timing of first relapse.139 Thus, among patients with pre-B-cell ALL in second CR after early bone marrow relapse, TBI-containing allogeneic HCT may improve outcomes compared with chemotherapy alone; however, for patients with late bone marrow relapse, HCT may offer no advantage over chemotherapy regimens.

An earlier BFM study (BFM-87) evaluated long-term outcomes with intensive chemotherapy or HCT (for poor prognosis disease) in patients with ALL relapsing after frontline treatment (\( n = 207 \); age, to 18 years).101 In this study, patients with poor prognosis included those with early bone marrow relapse (defined as relapse occurring during therapy or up to 6 months after completion of frontline treatment) or T-cell ALL. The 15-year EFS and OS rates for the entire patient cohort were 30% and 37%, respectively.101 The 10-year EFS rate was significantly higher among the patients who received allogeneic HCT after second CR (\( n = 27 \)) compared with those who received chemotherapy/radiotherapy only (\( n = 145 \); 59% vs 30%; \( P = .026 \)). All recipients of allogeneic HCT received TBI as part of the conditioning regimen. Based on multivariate regression analysis, the timing and site of relapse (with early relapse and isolated bone marrow relapse associated with poor outcomes), T-cell lineage disease, and HCT were significant independent predictors of EFS outcomes.101

The more recent BFM study (BFM-90) in patients with ALL relapsing after frontline therapy (\( n = 525 \); age, 1–18 years) further confirmed the benefits of allogeneic HCT in second CR.102 In this study, the timing of first relapse was defined as very early (within 18 months from initial diagnosis), early (>18 months from initial diagnosis and <6 months after completion of frontline therapy), and late (>6 months after completion of frontline treatment). The overall 10-year EFS and OS rates were 30% and 36%, respectively.102 Among the patients with high-risk disease (ie, presence of early isolated bone marrow relapse, early combined bone marrow and extramedullary relapse, very early bone marrow relapse, or T-cell lineage ALL regardless of relapse timing), patients who received chemoradiotherapy alone had a significantly shorter 10-year EFS (\( n = 76 \); 20%) than those who received HCT (\( n = 84 \); 33%; \( P < .005 \)) or the subgroup of patients who received HLA-compatible allogeneic HCT (\( n = 53 \); 40%; \( P < .001 \)). This EFS benefit with HCT (or with allogeneic HCT) was not observed among the subgroup of patients with intermediate-risk disease (ie, late bone marrow relapse or isolated extramedullary relapse regardless of relapse timing). The preferred conditioning regimen for HCT in this study included TBI.102

Seemingly contradictory data reported in the COG study CCG-1952, showed that prognosis after...
early bone marrow relapse in patients with standard-risk ALL (age 1 to <10 years of age and WBC count <50 X 10^9/L) remained poor with no apparent advantage of HCT, regardless of timing (eg, early or late) of bone marrow relapse.\textsuperscript{103} No significant differences were observed in the EFS or OS rates between treatment with HCT (n = 77) or chemotherapy (n = 81); the 2-year estimated EFS rates with HCT and chemotherapy were 49.5% and 49%, respectively (P=.39). Moreover, no significant differences in EFS rates were observed in the subgroup of patients with early or late bone marrow relapses.\textsuperscript{103} However, data were not available on the conditioning regimen used for HCT in this study for comparison with other trials.

A recent meta-analysis of 13 studies (n = 2962 patients) with Ph-negative ALL compared standard postremission therapy to determine if there is an advantage in survival among allogeneic HCT, autologous HCT or chemotherapy.\textsuperscript{140} In this analysis, patients younger than 35 years of age had a significant survival advantage when receiving a matched sibling donor compared to autologous HCT (odds ratio [OR], 0.79; 95% CI, 0.70–0.90; P=.0003). This advantage was not maintained in patients who were 35 years of age or older (OR, 1.01; 95% CI, 0.85–1.19; P=.9), a difference attributed to a higher absolute risk of nonrelapse mortality for older patients. There was a trend towards an inferior survival in patients receiving autologous HCT compared to chemotherapy (OR, 1.18; 95% CI, 0.99–1.41; P=.06) though statistical significance was not reached. Similarly, a meta-analysis including 14 trials found that the 5-year leukemia-free survival was higher following allogeneic transplantation (45%; 95% CI, 38%–51%) compared to autologous transplant or chemotherapy (30%; 95% CI, 23%–37%).\textsuperscript{141}

**NCCN Recommendations for Ph-Negative ALL**

**AYA Patients (Age 15–39 Years) with Ph-Negative ALL:** For patients with relapsed/refractory disease after an initial CR, participation in a clinical trial is preferred, when possible. In the absence of an appropriate trial, patients may be considered for second-line therapy with induction regimens not previously used, subsequent chemotherapy (with regimens containing clofarabine, nelarabine [for T-cell ALL], VSLI, cytarabine, or alkylating agents), or allogeneic HCT if a donor is available. For patients with Ph-negative precursor B-cell ALL, blinatumomab should be considered (see ALL-D 3 of 4, page 1254).

**Adult Patients (Age ≥40 Years) with Ph-Negative ALL:** For patients with relapsed/refractory disease after an initial CR, participation in a clinical trial is preferred, when possible. In the absence of an appropriate trial, patients may be considered for second-line therapy with induction regimens not previously used, subsequent chemotherapy (with regimens containing clofarabine, nelarabine [for T-cell ALL], VSLI, cytarabine, or alkylating agents), or allogeneic HCT (if a donor is available) in those physically fit enough to undergo transplantation. For patients with Ph-negative precursor B-cell ALL, blinatumomab may be considered.(see ALL-D 3 of 4, page 1254).

**Role of MRD Evaluation**

MRD in ALL refers to the presence of leukemic cells below the threshold of detection using conventional morphologic methods. Patients who experienced a CR according to morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow: up to 10^{10} malignant cells.\textsuperscript{79,142}

The most frequently used methods for MRD assessment include multicolor flow cytometry to detect abnormal immunophenotypes and PCR assays to detect clonal rearrangements in immunoglobulin heavy chain genes and/or T-cell receptor genes. Current flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of fewer than 1 X 10^4 (<0.01%) bone marrow mononuclear cells (MNCs). The concordance rate for detecting MRD between these methods is high. In a study that analyzed MRD using both flow cytometry and PCR techniques in 1375 samples from 227 patients with ALL, the concordance rate for MRD assessment (based on a detection threshold of <1 X 10^4 for both methods) was 97%.\textsuperscript{143} The combined or tandem use of both methods would allow for MRD monitoring in all patients, thereby avoiding potential false-negative results.\textsuperscript{143,144} Numerous studies in both childhood and adult ALL have shown the prognostic importance of postinduction (and/or postconsolidation) MRD measurements in predicting the likelihood of disease relapse. New multiplexed PCR and next-generation sequencing for MRD are emerging methodologies. Currently these
techniques may be labor- and resource-intensive for routine application in the clinical practice setting.

**MRD Assessment in Childhood ALL**

Among children with ALL who experience a CR according to morphologic evaluation after induction therapy, approximately 25% to 50% may still have detectable MRD based on sensitive assays (in which the threshold of MRD negativity is $<1 \times 10^{-4}$ bone marrow MNCs). An early study in children with ALL (n = 178) showed that patients with detectable MRD after initial induction therapy (42% of patients) had significantly shorter time to relapse than patients with MRD-negative status ($P<.001$), defined by a PCR sensitivity level of less than $1.5 \times 10^{-4}$. Patients with MRD after induction had a 10-fold increase in risk of death compared with those without detectable MRD. Moreover, the level of detectable MRD was found to correlate with relapse; patients with MRD of $1 \times 10^{-2}$ or greater had a 16-fold higher risk of relapse compared with those who had MRD levels less than $1 \times 10^{-3}$. In another study in children with ALL (n = 158), patients with detectable MRD (flow cytometry sensitivity level $<1 \times 10^{-4}$) at the end of induction therapy had a significantly higher 3-year cumulative incidence of relapse than those who were MRD negative (33% vs 7.5%; $P<.001$). Subsequent studies have confirmed these findings. In a study of 165 patients, the 5-year relapse rate was significantly higher among patients with MRD (flow cytometry sensitivity $<1 \times 10^{-4}$) versus those without detectable disease (43% vs 10%; $P<.001$). In addition, the persistence of MRD during the course of therapy was associated with risk of relapse; the cumulative rate of relapse was significantly higher among patients with MRD persisting through week 14 of continued treatment compared with patients who became MRD-negative by 14 weeks (68% vs 7%; $P=.035$). MRD evaluation was shown to be a significant independent predictor of outcome.

MRD assessments at an earlier time point in the course of treatment (eg, during induction therapy) have been shown to be highly predictive of outcomes in children with ALL. In one study, nearly 50% of patients had MRD clearance (MRD $<1 \times 10^4$ by flow cytometry) before day 19 of induction therapy (about 2–3 weeks from initiation of induction); the 5-year cumulative incidence of relapse was significantly higher among patients with MRD at day 19 of treatment than those without detectable MRD (33% vs 6%; $P<.001$). More recently, the prognostic significance of MRD detection at lower levels (sensitivity threshold, $\leq 1 \times 10^{-5}$, or $\leq 0.001\%$, according to PCR measurements) was evaluated in children with B-cell lineage ALL treated with contemporary regimens. At the end of induction therapy, 58% of patients had undetectable disease based on PCR values. Among the remaining patients with detectable MRD, 17% had MRD of 0.01% or greater, 14% had less than 0.01% (but $\geq 0.001\%$), and 11% had less than 0.001%. The 5-year cumulative incidence of relapse was significantly higher among patients with MRD of 0.01% or greater versus patients with less than 0.01% or undetectable disease (23% vs 6%; $P<.001$). Furthermore, the 5-year cumulative incidence of relapse was significantly higher among the subgroup of patients with MRD less than 0.01% (but $\geq 0.001\%$) versus those with MRD less than 0.001% or undetectable disease (13% vs 5%; $P<.05$). MRD status at the end of induction therapy strongly correlated with MRD levels (flow cytometry sensitivity level <0.01%) at day 19 during induction; all patients who had MRD of 0.01% or greater at the end of induction had MRD of 0.01% or greater at day 19. Although this study showed that a higher risk of relapse was seen among patients with MRD below the generally accepted threshold level (<0.01% but $\geq 0.001\%$) compared with those with very low MRD (<0.001%) or no detectable disease, further studies are warranted to determine whether this threshold should be used to risk stratify patients or guide decisions surrounding treatment intensification.

In one of the largest collaborative studies conducted in Europe (the AIEOP-BFM ALL 2000 study), children with Ph-negative B-cell lineage ALL (n = 3184 evaluable) were risk stratified according to MRD status (PCR sensitivity level $\leq 0.01\%$) at 2 time points (days 33 and 78) which were used to guide postinduction treatment. Patients were considered standard risk if MRD negativity ($\leq 0.01\%$) was achieved at both days 33 and 78, intermediate risk if MRD was greater than 0.01% (but $<0.1\%$) on either day 33 or 78 (the other time point being MRD-negative) or on both days 33 and 78, and high risk if MRD was 0.1% or greater on day 78. Nearly all patients with favorable cytogenetic/molecular markers such as the ETV6-RUNX1 subtype or hyperdiploidy were either standard risk or intermediate risk.
based on MRD evaluation.\textsuperscript{150} The 5-year EFS rate was 92% for patients categorized as standard risk (n = 1348), 78% for intermediate risk (n = 1647), and 50% for high risk (n = 189; P<.001); the 5-year OS rates were 98%, 93%, and 60%, respectively. MRD-based risk stratification significantly differentiated risks for relapse (between standard- and intermediate-risk subgroups) even among patient populations with \textit{ETV6-RUNX1} or hyperdiploidy. Importantly, in this large-scale study, MRD remained a significant and powerful independent prognostic factor for relapse in the overall population.\textsuperscript{150}

A randomized controlled trial in children and young adults with low-risk ALL according to MRD, compared treatment reduction to standard induction (n = 521).\textsuperscript{151} Patients were randomized to receive either one or two delayed intensification courses consisting of pegaspargase on day 4; vincristine, dexamethasone (alternate weeks), and doxorubicin for 3 weeks; and 4 weeks of cyclophosphamide and cytarabine. The 5-year EFS between the 2 cohorts were not statistically significant (94.4% vs 95.5%; OR, 1; 95% CI, 0.43–2.31; 2-sided P=.99). No statistical difference was seen regarding relapse or serious adverse events; however, there was a singular treatment-related death in the second delayed intensification cohort and 74 episodes of grade 3 or 4 toxic events. The results suggest that treatment reduction is reasonable for children and young adults with ALL who have a low risk of relapse based on MRD at the end of induction.

A recent randomized study investigated whether improved outcome could be seen with augmented postremission therapy for children and young adults stratified by MRD.\textsuperscript{152} In this trial, 533 patients with a high risk of MRD (defined as clinical standard-risk and intermediate-risk patients with MRD of 0.01% or higher at day 29 of induction) were randomized to receive standard therapy or augmented postremission therapy. The augmented treatment regimen included 8 doses of pegaspargase, 18 doses of vincristine, and escalated-dosing of intravenous methotrexate without folic acid rescue during the interim maintenance courses. The 5-year EFS was higher in patients receiving the augmented regimen versus the standard treatment group (89.6% vs 82.8%; OR, 0.61; 95% CI, 0.39–0.98; P=.04). However, it should be noted that more adverse events were seen with the augmented regimen and no statistically significant benefit was seen in OS at 5 years (92.9% vs 88.9%; OR, 0.67; 95% CI, 0.38–1.17; P=.16).

Stratification based on MRD may also indicate which patients should undergo allogeneic HCT versus continued chemotherapy. Children with an intermediate-risk of relapse based on MRD were stratified based on a cutoff MRD level of 10\textsuperscript{–3}.\textsuperscript{153} Patients with greater than or equal to MRD of 10\textsuperscript{–3} were allocated to receive HCT (n = 99). In this group, 83% had donors and underwent HCT versus 17% who had no suitable donor and therefore continued chemotherapy. The EFS was higher for patients receiving HCT (64% ± 5%) versus patients remaining on chemotherapy (24% ± 10%). Patients that had a low level of MRD (less than 10\textsuperscript{–3}) were directed to receive continued chemotherapy (n = 109). Within this cohort, 83 patients received either chemotherapy or radiotherapy alone and 22 patients received an allogeneic HCT. No significant difference in EFS was seen between these 2 groups (66% ± 6% vs 80% ± 9%; P=.45). Results indicate that MRD can be useful to further risk stratify patients with intermediate risk of relapse to the appropriate treatment regimen. However, the study acknowledges that cutoff values for MRD are regimen dependent as indicated by the divergence from the earlier ALL R3 trial. While the earlier trial also advocated the use of MRD to stratify patients for HCT, a higher threshold for MRD level was used (10\textsuperscript{–4}), a difference that may reflect the more intensive induction regimen.\textsuperscript{154} Therefore MRD levels may influence treatment decisions, but the application of this prognostic factor must be carefully evaluated on a regimen by regimen basis.

Approximately 20% of children treated with intensive therapies for ALL will ultimately experience disease relapse.\textsuperscript{155} MRD assessment may also play a prognostic role in the management of patients in the relapsed setting.\textsuperscript{156,157} In patients (n = 35) who experienced a second remission (morphologic CR) after reinduction treatment, MRD (flow cytometry sensitivity level <0.01%) after reinduction (day 36) was significantly associated with risks for relapse; the 2-year cumulative incidence of relapse was 70% among patients with MRD of 0.01% or greater versus 28% among those with MRD less than 0.01% (P=.008).\textsuperscript{156} In addition, among the subgroup of patients who experienced first relapse after cessation of treatment, the 2-year cumulative incidence of second relapse was 49% among those with MRD of 0.01%
or greater versus 0% for those with MRD less than 0.01% (P=.014). Both the presence of MRD at day 36 of reinduction therapy and at first relapse occurring during therapy, were significant independent predictors of second relapse based on multivariate analysis.\(^{156}\) In another study, MRD (PCR sensitivity level <0.01%) was evaluated in high-risk children with ALL (n = 60) who experienced first relapse within 30 months from the time of diagnosis.\(^{157}\) Categories based on MRD evaluation after the first chemotherapy cycle (3–5 weeks after initiation of reinduction treatment) included MRD negativity (undetectable MRD), MRD positive but unquantifiable (levels <0.01%), and MRD of 0.01% or greater. The 3-year EFS rate based on these MRD categories was 73%, 45%, and 19%, respectively (P<.05).\(^{157}\) Thus, MRD assessment can identify patients with a high probability of second relapse, which may offer an opportunity for risk-adapted second-line treatment strategies in these patients.

Several studies suggest early assessment of MRD during induction treatment (eg, day 15 from initiation of treatment) may be highly predictive of subsequent relapse in children with ALL.\(^{158,159}\) This raises the possibility of identifying patients with high-risk disease who may potentially benefit from earlier intensification or tailoring of treatment regimens, or for potentially allowing less-intensive treatments to be administered in patients at low risk for relapse based on early MRD measurements. Large trials are warranted to address these possibilities, although serial MRD measurements may likely be needed to monitor leukemic cell kinetics during the long course of treatment.

### MRD Assessment in Adult ALL

Studies in adults with ALL have shown the strong correlation between MRD and risk for relapse, and the prognostic significance of MRD measurements during and after initial induction therapy.\(^{160-163}\) In an analysis of postinduction MRD (flow cytometry sensitivity level <0.05%) in adult patients with ALL (n = 87), median RFS was significantly longer among patients with MRD less than 0.05% at day 35 compared with those with MRD of 0.05% or greater (42 vs 16 months; P=.001).\(^{163}\) A similar pattern emerged when only the subgroup of patients with morphologic CR at day 35 was included in the MRD evaluation. Although patient numbers were limited, 90% of patients with MRD less than 0.03% at an earlier time point (day 14 during induction therapy) remained relapse-free at 5 years.\(^{161}\) MRD after induction therapy was a significant predictor of relapse in a subgroup analysis from the MRC UKALL/ECOG study of patients with Ph-negative B-cell lineage ALL (n = 161).\(^{162}\) The 5-year RFS rate was significantly higher in patients with MRD negativity versus those with MRD of 0.01% or greater (71% vs 15%; P=.0002).\(^{162}\)

Postinduction MRD can serve as an independent predictor of relapse even among adult patients considered to be standard risk based on traditional prognostic factors. In a study of adult patients with Ph-negative ALL (n = 116), MRD status after induction therapy (flow cytometry sensitivity level <0.1%) was significantly predictive of relapse regardless of whether the patient was standard risk or high risk at initial evaluation.\(^{161}\) Among patients who were initially classified as standard risk, those with MRD of less than 0.1% after induction had a significantly lower risk of relapse at 3 years compared with patients who had higher levels of MRD (9% vs 71%; P=.001). Interestingly, MRD measured during the postconsolidation time point was not significantly predictive of outcomes.\(^{161}\) In the German Multicenter ALL (GMALL) 06/99 study, patients with standard-risk disease (n = 148 evaluable) were monitored for MRD (PCR sensitivity level <0.01%) at various time points during the first year of treatment.\(^{160}\) Only patients with ALL who met all of the following criteria for standard risk were enrolled in this study: absence of t(4;11) MLL translocation or t(9;22) BCR-ABL translocation; WBC count less than 30 × 10^9/L for B-cell lineage ALL or less than 100 × 10^9/L for T-cell lineage ALL; age 15 years to 65 years; and achievement of morphologic CR after phase I of induction treatment. At the end of initial induction therapy (day 24), patients with MRD of 0.01% or greater had a 2.4-fold higher risk (95% CI, 1.3–4.2) of relapse than those with MRD of less than 0.01%.\(^{160}\) Moreover, this study identified distinct risk groups according to MRD status at various time points. Patients categorized as low risk (10% of study patients) had MRD of less than 0.01% at both days 11 and 24 (during and after initial induction), and had 3-year DFS and OS rates of 100% (for both endpoints). Patients in the high-risk group (23%) had MRD of 0.01% or greater persisting through week 16, and 3-year DFS and OS rates of 6% and 45%,
respectively. All other patients (67%) categorized as intermediate risk had 3-year DFS and OS rates of 53% and 70%, respectively.\(^\text{160}\) Importantly, a multivariate Cox regression analysis that included gender, age, WBC count, B- or T-cell lineage, and MRD in the model showed that MRD was the only independently significant predictor of outcome in this patient population.

A recent prospective study (Japan ALL MRD2002) evaluated outcomes by MRD status in adult patients with Ph-negative ALL.\(^\text{164}\) Among the patients who achieved a CR after induction/consolidation (n = 39), those who were MRD negative (<0.1%) after induction had a significantly higher 3-year DFS (69% vs 31%; \(P=0.04\)) compared with patients who were MRD positive; 3-year OS was higher among patients with MRD-negative status after induction, although the difference was not statistically significant (85% vs 59%). Based on multivariate Cox regression analysis, older age (>35 years) and MRD positivity after induction were significant independent factors predictive of decreased DFS. WBC counts and MRD status after consolidation were not significant predictors of DFS outcomes.\(^\text{164}\) Thus, MRD evaluation postinduction may provide additional risk stratification criteria among patients who would otherwise be considered standard risk according to traditional evaluation of prognostic factors.

MRD assessment after consolidation therapy has been shown to have prognostic significance, offering the possibility to adjust post-consolidation treatment approaches. In a study that evaluated MRD (PCR sensitivity level <0.01%) after consolidation therapy (weeks 16–22 from initiation of induction) in adult patients with ALL (n = 142), patients with MRD of less than 0.01% (n = 58) were primarily allotted to receive maintenance chemotherapy for 2 years, whereas those with MRD of 0.01% or greater (n = 54) were eligible to undergo allogeneic HCT after high-dose therapy.\(^\text{165}\) The 5-year DFS rate was significantly higher among patients with MRD negativity versus those with MRD of 0.01% or greater (72% vs 14%; \(P=0.001\)); similarly, the 5-year OS rate was significantly higher for patients with MRD-negative status post-consolidation (75% vs 33%; \(P=0.001\)).\(^\text{165}\) In a followup to the GMALL 06/99 study mentioned earlier, patients with standard-risk ALL (as defined by Bruggemann et al\(^\text{169}\)) who experienced MRD negativity (PCR sensitivity <0.01% leukemic cells) during the first year of treatment underwent sequential MRD monitoring during maintenance therapy and followup.\(^\text{166}\) Among the patients included in this analysis (n = 105), 28 (27%) became MRD-positive after the first year of therapy; MRD was detected before hematologic relapse in 17 of these patients.\(^\text{166}\) The median RFS was 18 months (calculated from the end of initial treatment) among the subgroup that became MRD-positive, whereas the median RFS has not yet been reached among patients who remained MRD-negative. The median time from MRD positivity (at any level, including nonquantifiable cases) to clinical relapse was 9.5 months; the median time from quantitative MRD detection to clinical relapse was only 4 months.\(^\text{166}\) Detection of postconsolidation MRD was highly predictive of subsequent hematologic relapse and introduced the concept of molecular relapse in ALL.

A subsequent analysis by GMALL investigators evaluated the potential advantage of intensifying or modifying treatment regimens (eg, incorporation of allogeneic HCT) based on postconsolidation MRD status. In one of the largest studies to assess the prognostic impact of MRD on treatment outcomes in adult patients with Ph-negative ALL (n = 580 with CR and evaluable MRD results; patients from GMALL 06/99 and 07/03 studies; age 15–55 years), molecular CR (defined as MRD <0.01%) after consolidation was associated with significantly higher probabilities of 5-year continuous CR (74% vs 35%; \(P<.0001\)) and OS (80% vs 42%; \(P=.0001\)) compared with molecular failure (MRD ≥0.01%).\(^\text{167}\) Based on multivariate analysis, molecular response status was a significant independent predictor of both 5-year continuous CR and OS outcomes. Among the patients with disease that did not result in a molecular CR, the subgroup who underwent allogeneic HCT in clinical CR (n = 57) showed a significantly higher 5-year continuous CR (66% vs 12%; \(P<.0001\)) and a trend for higher OS (54% vs 33%; \(P=.06\)) compared with the subgroup without HCT (n = 63).\(^\text{167}\) In this latter subgroup of patients with disease that did not result in a molecular CR and who did not undergo HCT, the median time from MRD detection to clinical relapse was approximately 8 months.\(^\text{167}\) This analysis showed that MRD status after consolidation was an independent risk factor for poorer outcomes in adults with ALL and may identify high-risk patients who could potentially benefit from allogeneic HCT.
Studies in children and adult patients with ALL suggest that differences may exist in the kinetics of leukemic cell eradication. Among children treated on contemporary regimens, 60% to 75% experienced clearance of MRD at the end of induction therapy (typically 5–6 weeks after initiation of induction). In one study, nearly 50% of children had MRD clearance (<0.01% by flow cytometry) at day 19 of induction therapy. Adult patients seem to have a slower rate of leukemic cell clearance compared with children, with 30% to 50% of adult patients having MRD negativity after initial induction. Approximately 50% of cases remained MRD positive at 2 months after initiation of induction, with further reductions in the proportion of MRD-positive cases occurring beyond 3 to 5 months. Possible determinants for differences in the kinetics of leukemic cell reduction in the bone marrow may be attributed to the therapeutic regimens, variations in the distribution of immunophenotypic or cytogenetic/molecular features, and other host factors.

**NCCN Recommendations for MRD Assessment**

Collectively, studies show the high prognostic value of MRD in assessing risk for relapse in patients with ALL, and the role of MRD monitoring in identifying subgroups of patients who may benefit from further intensified therapies or alternative treatment strategies. Flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of fewer than 1 × 10^−4 (<0.01%) bone marrow MNCs. The concordance rate for detecting MRD between these methods is high. However, high-sensitivity PCR assays (for analysis of immunoglobulin or T-cell receptor gene rearrangements) require the identification of patient-specific markers that involve direct sequencing, and may therefore be labor- and resource-intensive for routine application in the clinical practice setting. Recommendations for the minimal technical requirements for MRD assessment (both for PCR and flow cytometry methods) and definitions for response based on MRD results (eg, MRD negativity, nonquantifiable MRD positivity, quantifiable MRD positivity) were published as a result of a consensus meeting held by ALL study groups across Europe. The recommendations were made in an effort to standardize MRD measurements and reporting of data within the context of clinical trials. The panel strongly recommends that MRD assessments be performed at specialized treatment centers with access to Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories that have expertise in MRD assays (see ALL-F, page 1257).

The timing of MRD assessment varies depending on the ALL treatment protocol used, and may occur during or after completion of initial induction therapy. Therefore, it is recommended that the initial measurement be performed on completion of induction therapy; additional time points for MRD evaluation may be useful depending on the treatment protocol or regimen used. For MRD evaluation by multicolor flow cytometry, sampling of bone marrow MNCs is preferred over peripheral blood samples. At least 1 × 10^6 MNCs are required for analysis (approximately 2 mL of bone marrow or 5–10 mL of peripheral blood provide a sufficient number of cells for multiple analysis). For MRD evaluation with the real-time quantitative PCR assay, sampling of bone marrow MNC is preferred. At least 1 × 10^6 MNCs are required for initial marker characterization and generation of individual dilution series; 1 × 10^6 MNCs are sufficient for follow-up analysis. The minimal limit of assay sensitivity (to declare MRD negativity) should be less than 1 × 10^−4 (<0.01%).

**Summary**

The heterogeneous nature of ALL complicates the treatment of this hematologic disease. However, survival outcomes in patients with ALL continue to improve with the identification and incorporation of cytogenetic abnormalities and their prognostic relevance. Newer treatment options and refinement of the application of current strategies will also improve the treatment of patients with ALL. The recent inclusion of immunotherapy treatments including CAR T cells and blinatumomab may improve outcomes for patients with relapsed/refractory disease. Other improvements have been seen with second-generation TKIs that overcome some of the limitations of the first-generation TKIs. Furthermore, MRD monitoring is modifying treatment strategies. Although this highlights only some of the recent developments, it is evident that advancement in a multitude of different areas is integral for the continued improvement in the treatment of ALL.

**References**

Acute Lymphoblastic Leukemia, Version 2.2015


Tachibana T, Numata A, Tanaka M, et al. Successful treatment with dasatinib and allogeneic peripheral blood stem cell transplant for imatinib-


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

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<td>Hagop M. Kantarjian, MD</td>
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<td>Rebecca B. Klisovic, MD</td>
<td>Gilead; and Novartis Pharmaceuticals Corporation</td>
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<td>Gary Kupfer, MD</td>
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<td>Lawyer</td>
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<td>Mark Litzow, MD</td>
<td>Amgen Inc.; Sigma-Tau Pharmaceuticals, Inc.; and Spectrum Pharmaceuticals</td>
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<td>Arthur Liu, MD, PhD</td>
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<td>Arati V. Rao, MD</td>
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<td>Bijal Shah, MD</td>
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<td>Geoffrey L. Uy, MD</td>
<td>Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals, Inc.; and sanofi-aventis U.S.</td>
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<td>Eunice S. Wang, MD</td>
<td>None</td>
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<td>Andrew D. Zelenetz, MD, PhD</td>
<td>Abbott Laboratories; Boehringer Ingelheim GmbH; Celgene Corporation; Constellation Pharmaceuticals; Curis; Genentech, Inc.; Gilead; Infinity; Janssen Pharmaceutica Products, LP; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals, Inc.; and Seattle Genetics</td>
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Courtney Smith, PhD, Scientist, NCCN, has disclosed that she has an Employment/Governing Board, Patent, Equity, or Royalty conflict with Johnson & Johnson and OPKO; she has a Spouse/Domestic Partner/Dependent Potential Conflict with Ethos Health Communications and Complete Healthcare Communications. The remaining NCCN Guidelines staff have no conflicts to disclose.