

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# **Acute Lymphoblastic Leukemia**

Version 1.2014

**NCCN.org**

**Continue**

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

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical\\_trials/physician.html](#).

**NCCN Categories of Evidence and Consensus:** All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Evidence and Consensus](#).

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Summary of changes in the 1.2014 version of the NCCN Acute Lymphoblastic Leukemia Guidelines from the 3.2013 version include:

### [ALL-4](#)

- Footnote “t” is new to the page: Allogeneic HSCT may be considered based on performance status, comorbidities, availability of appropriate transplant donor, and transplant center expertise in treating older patients with allogeneic HSCT.

### [ALL-A](#)

- The following immunophenotype added for ETP 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

### [ALL-B 1 of 4](#)

- The following bullet was added:  
**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.

### [ALL-D 1 of 4](#)

- Single agent dasatinib was removed as a treatment option for Adult patients aged  $\geq 40$  years with Ph-positive ALL.
- Footnote “c” modified: *Dose modifications for antimetabolites in maintenance should be consistent with the chosen treatment regimen. It may be necessary to reduce dose/eliminate antimetabolite in the setting of myelosuppression and/or hepatotoxicity.*

### [ALL-F](#)

- Bullet 2 added: 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.

### [MS-1](#)

- The Discussion section was updated to reflect changes in the algorithm.

### DIAGNOSIS

Acute lymphoblastic leukemia (ALL)<sup>a,b,c</sup>

The diagnosis of ALL generally requires demonstration of  $\geq 20\%$  bone marrow lymphoblasts<sup>d</sup> 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<sup>e</sup>

#### 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<sup>a</sup>
- Reverse transcriptase-polymerase chain reaction (RT-PCR) testing for fusion genes (eg, *BCR-ABL*)

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<sup>a</sup> and cytogenetic risk group<sup>f</sup>

**Strongly recommend that patients be treated in specialized centers**

[See Workup and Risk Stratification ALL-2](#)

<sup>a</sup>Subtypes: B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities include hyperdiploidy, hypodiploidy, and commonly occurring translocations: t(9;22)(q34;q11.2)[*BCR-ABL*1]; t(v;11q23)[*MLL* rearranged]; t(12;21)(p13;q22)[*TEL-AML*1]; t(1;19)(q23;p13.3)[*E2A-PBX*1]; t(5;14)(q31;q32)[*IL3-IGH*;relatively rare]. B-cell lymphoblastic leukemia/lymphoma, not otherwise specified. T-cell lymphoblastic leukemia/lymphoma.

<sup>b</sup>Criteria 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.

<sup>c</sup>Treatment of Burkitt leukemia/lymphoma – [see NCCN Guidelines for Non-Hodgkin's Lymphoma](#).

<sup>d</sup>While these guidelines pertain primarily to patients with leukemia, patients with lymphoblastic lymphoma (B- or T-cell) would likely also benefit from ALL-like regimens.

<sup>e</sup>[See Typical Immunophenotype by Major ALL Subtypes \(ALL-A\)](#).

<sup>f</sup>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): *TEL-AML*1;

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).

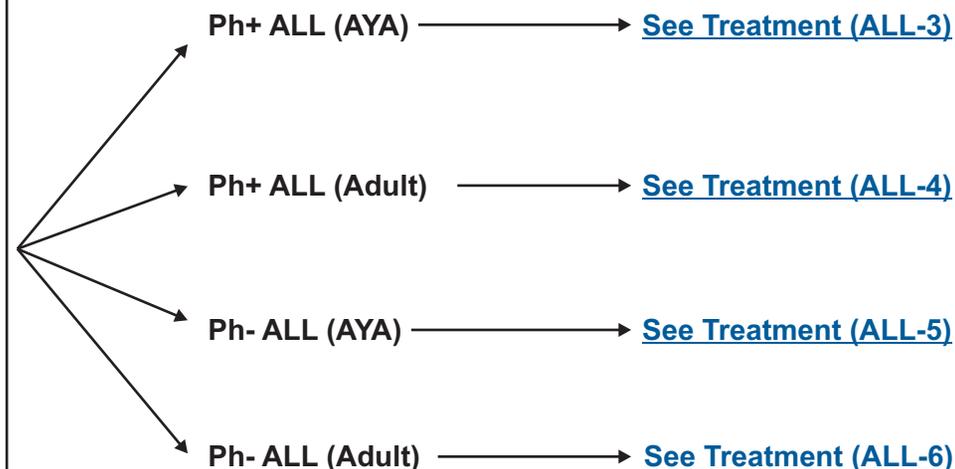
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## WORKUP<sup>g</sup>

- 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 panel: lactate dehydrogenase (LDH), uric acid, K, Ca, Phos (See Tumor Lysis Syndrome (TLS) in the [NCCN Guidelines for Non-Hodgkin Lymphoma Guidelines](#))
- CT/MRI of head, if neurologic symptoms<sup>h</sup>
- Lumbar puncture (LP)<sup>h,i</sup>
  - ◆ [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 (testicular involvement is especially common in T-ALL)
- 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](#))
- 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 stem cell transplant [HSCT])
- In patients with poor risk features who lack a sibling donor, consider early evaluation for an alternative donor search

## RISK STRATIFICATION



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

<sup>h</sup>For patients with major neurologic signs or symptoms at diagnosis, appropriate imaging studies should be performed to detect meningeal disease, choroidomas, or central nervous system (CNS) bleeding. [See Evaluation and Treatment of Extramedullary Involvement \(ALL-C\)](#)

<sup>i</sup>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.

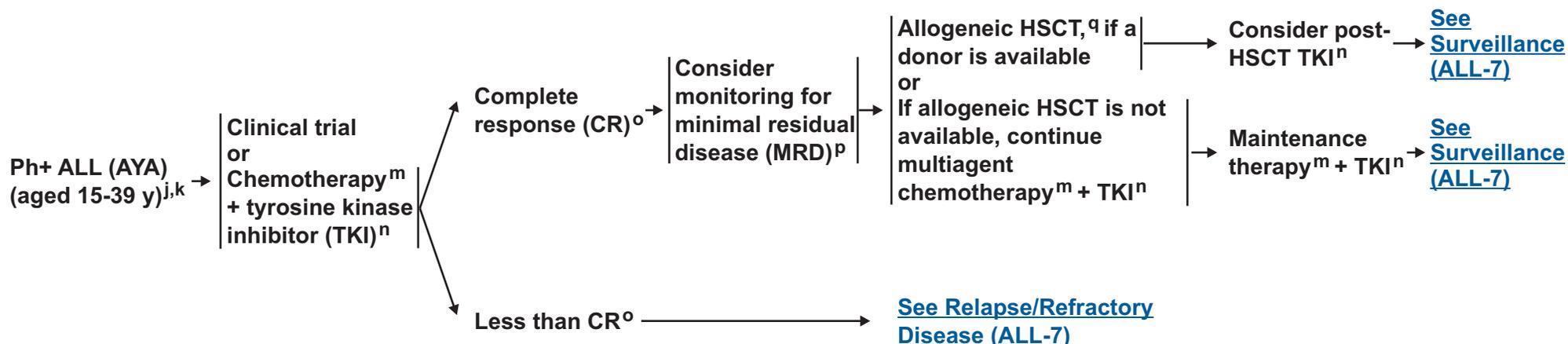
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**RISK STRATIFICATION**

**TREATMENT INDUCTION<sup>l</sup>**

**CONSOLIDATION THERAPY**



<sup>j</sup>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.

<sup>k</sup>For additional considerations in the management of AYA patients with ALL, see the [NCCN Guidelines for Adolescent and Young Adult Oncology](#).

<sup>l</sup>All ALL treatment regimens include CNS prophylaxis.

<sup>m</sup>[See Principles of Chemotherapy \(ALL-D\)](#).

<sup>n</sup>See [Discussion section](#) for use of different TKIs in front-line therapy.

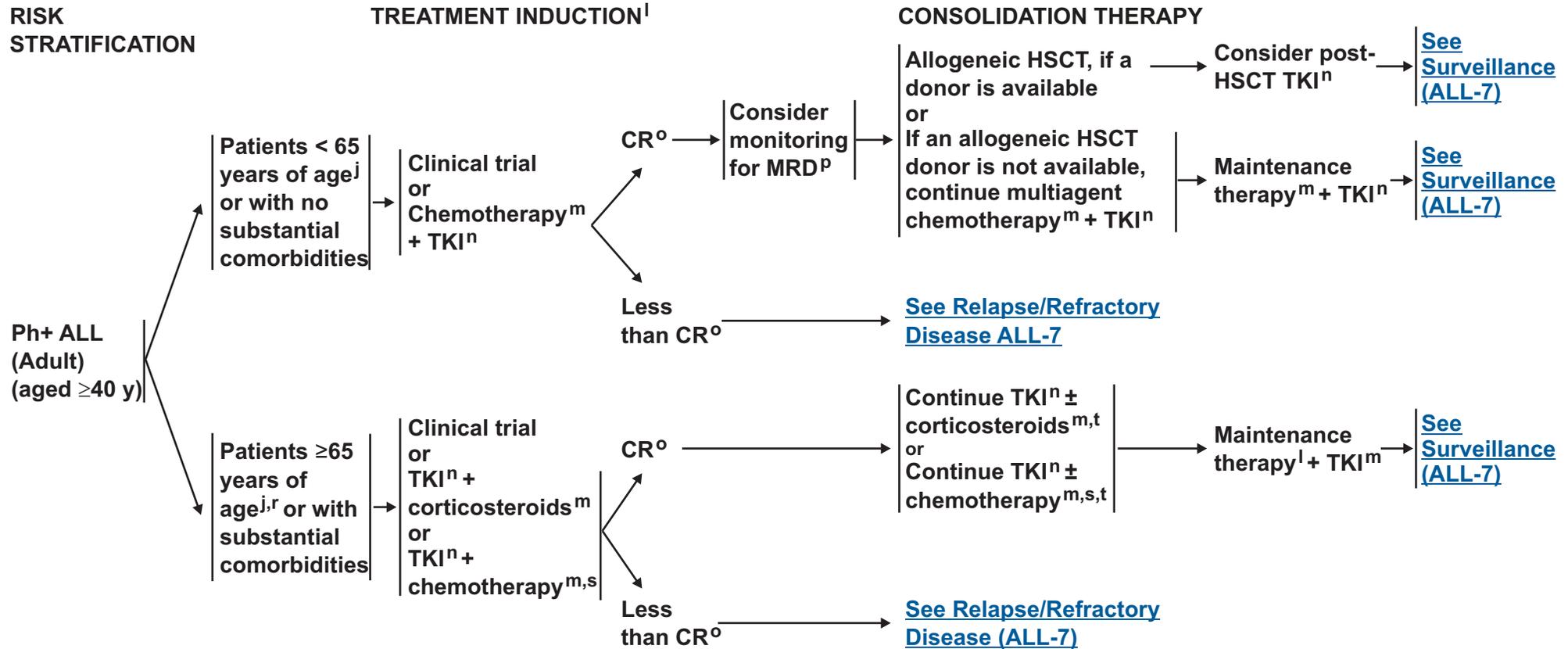
<sup>o</sup>[See Response Criteria \(ALL-E\)](#).

<sup>p</sup>[See Minimal Residual Disease Assessment \(ALL-F\)](#).

<sup>q</sup>Emerging data suggest that for younger patient (aged  $\leq 21$  y), allogeneic HSCT may not offer an advantage over chemotherapy + TKIs; Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. *J Clin Oncol* 2009;27:5175-5181.

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<sup>p</sup>[See Minimal Residual Disease Assessment \(ALL-F\)](#).

<sup>r</sup>For additional considerations in the management of senior adult patients with ALL, see the [NCCN Guidelines for Senior Adult Oncology](#).

<sup>s</sup>Consider dose modifications appropriate for patient age and performance status.

<sup>t</sup>Allogeneic HSCT may be considered based on performance status, comorbidities, availability of appropriate transplant donor, and transplant center expertise in treating older patients with allogeneic HSCT.

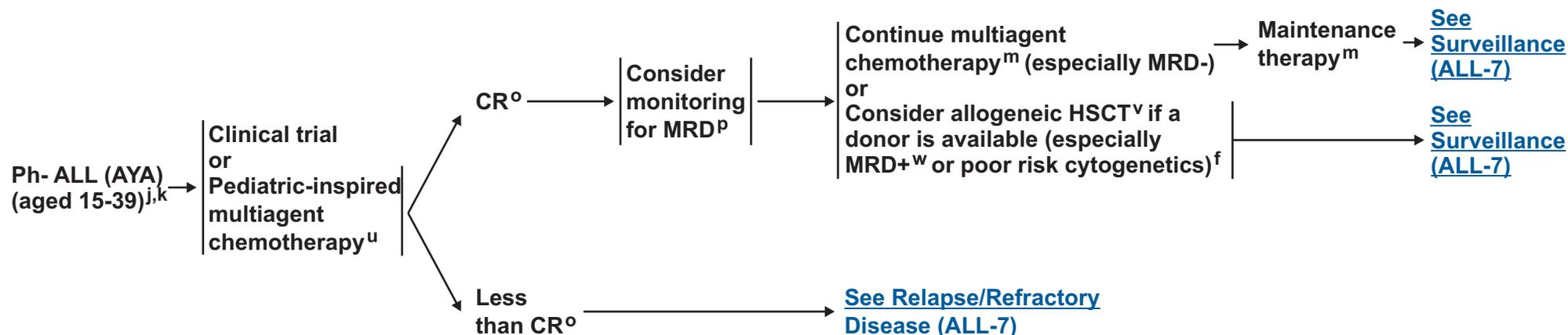
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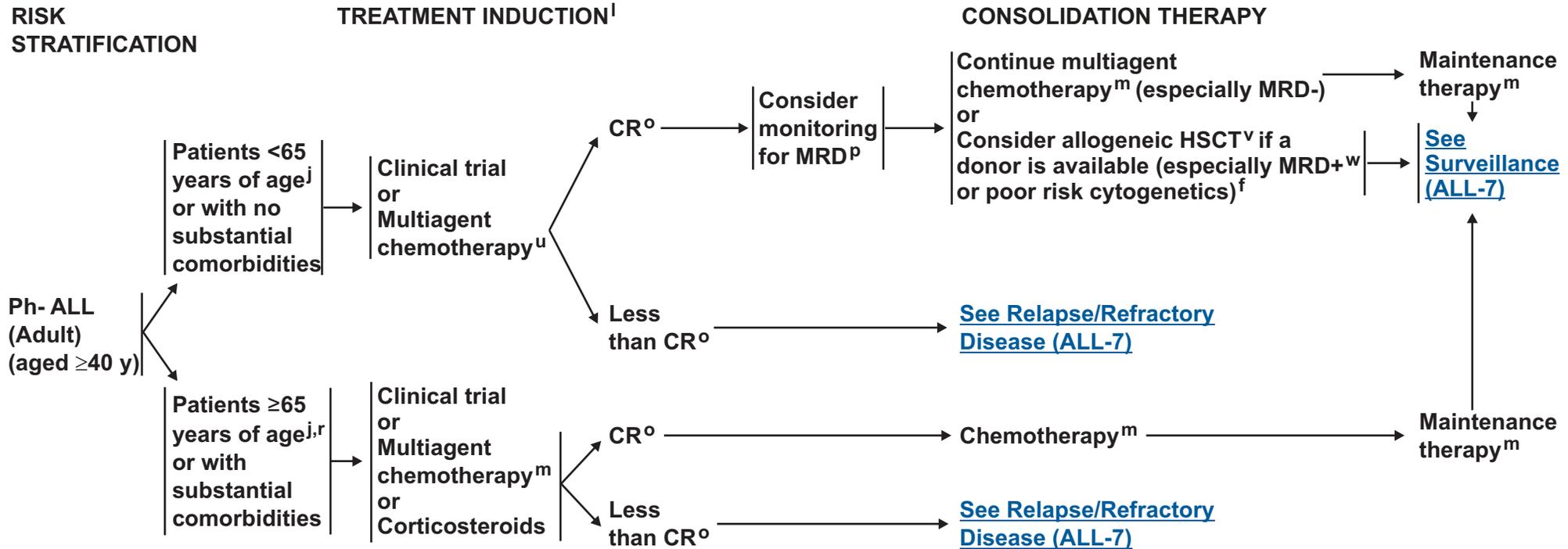
<sup>u</sup>[See Principles of Chemotherapy \(ALL-D\)](#). All regimens include induction/delayed intensification (especially for pediatric-inspired regimens) and maintenance therapy.

<sup>v</sup>Benefit with allogeneic HSCT is unclear in this setting.

<sup>w</sup>High WBC count ( $\geq 30 \times 10^9/L$  for B lineage or  $\geq 50 \times 10^9/L$  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.

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<sup>v</sup>Benefit with allogeneic HSCT is unclear in this setting.

<sup>w</sup>High WBC count (≥30 x 10<sup>9</sup>/L for B lineage or ≥50 x 10<sup>9</sup>/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.

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## SURVEILLANCE<sup>x</sup>

## RELAPSE/REFRACTORY DISEASE

## TREATMENT

### Year 1 (every 1-2 months):

- Physical exam, CBC with differential every month
- Liver functions 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:

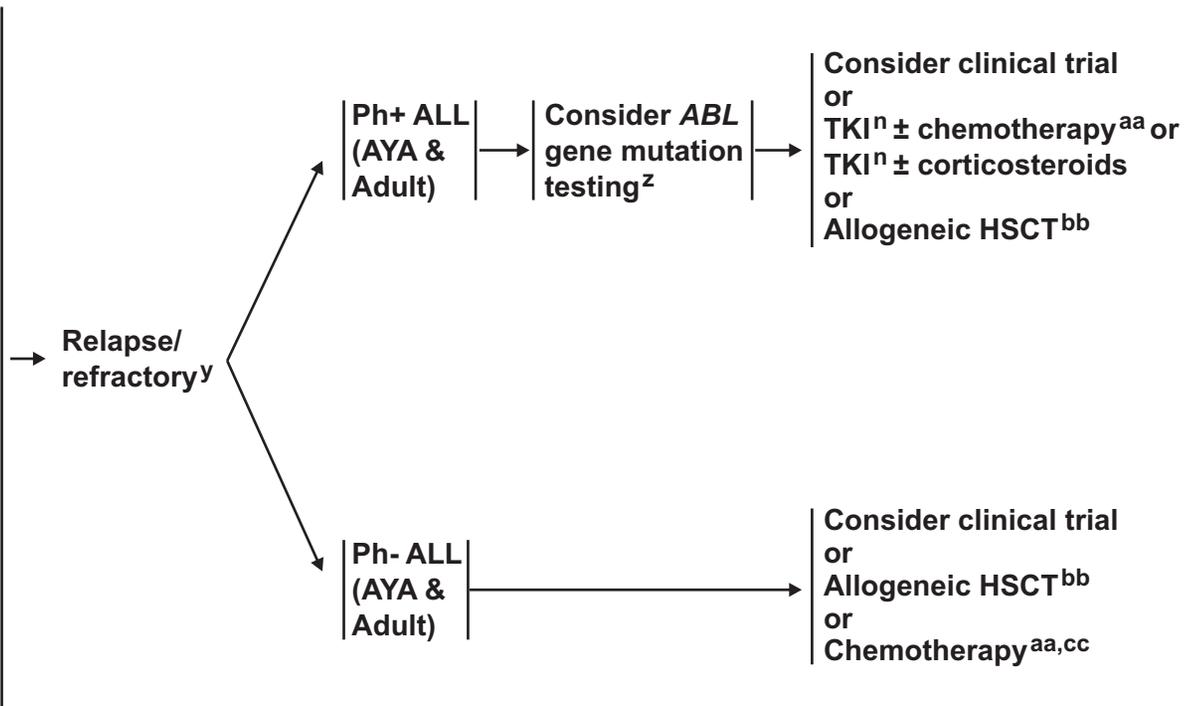
- Physical exam including testicular exam, CBC with differential every 3 months

### Year 3+:

- 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](#)

Refer to the ALL Long-term Follow-up Guidelines from Children's Oncology Group (COG): <http://www.survivorshipguidelines.org/>



<sup>n</sup>See [Discussion section](#) for use of different TKIs in this setting.

<sup>x</sup>Surveillance recommendations apply after completion of chemotherapy, including maintenance.

<sup>y</sup>Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.

<sup>z</sup>See [Treatment Options Based on BCR-ABL Kinase Domain Mutation Status \(ALL-D 3 of 4\)](#).

<sup>aa</sup>See Principles of Chemotherapy ([ALL-D 1 of 4](#) or [ALL-D 2 of 4](#) for regimens not previously used for induction therapy or [ALL-D 3 of 4](#) for regimens for relapsed/refractory ALL). Nelarabine is available for patients with relapsed T-ALL. Clofarabine is available for relapsed pre-B-ALL in patients age ≤ 21 y. Vincristine sulfate liposome injection is available for adult patients with Ph- ALL in ≥ second relapse or disease progression after ≥2 therapies.

<sup>bb</sup>For patients with relapsed disease after allogeneic HSCT, a second allogeneic HSCT and/or donor lymphocyte infusion (DLI) can be considered.

<sup>cc</sup>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<sup>1,2</sup>**

The initial immunophenotyping panel should be sufficiently comprehensive to establish a leukemia-associated phenotype (LAP) that may include expression of non-lineage antigens. These LAP are useful in classification, particularly mixed-lineage leukemias, and as a signature for minimal residual disease (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  $\mu$ +, slg-, CD10+/-**

**B-ALL with recurrent genetic abnormalities:**

- **Hyperdiploidy (DNA index >1.16; 51-65 chromosomes without structural abnormalities): CD10+, CD19+, CD34+, CD45-**
- **Hypodiploidy (<46 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  $\mu$ +**
- **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**

Borowitz MJ, Chan JKC. B lymphoblastic leukaemia/lymphoma, not otherwise specified; B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities; T lymphoblastic leukaemia/lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4th). Lyon: IARC; 2008:168-178.

<sup>1</sup>Criteria 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.

<sup>2</sup>Treatment of Burkitt leukemia/lymphoma – see [NCCN Guidelines for Non-Hodgkin's Lymphoma](#).

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### SUPPORTIVE CARE (1 of 4)

#### Best supportive care

- Infection control ([See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#))
  - ◆ Prophylactic anti-infectives
    - Antibacterial prophylaxis: consider fluoroquinolones
    - Antiviral prophylaxis: HSV prophylaxis (eg, acyclovir, famciclovir, valacyclovir); VZV prophylaxis (eg, acyclovir) for at least 1 year after HSCT in transplant patients; and HBV prophylaxis (eg, adefovir, entecavir, lamivudine) for at least 6-12 months after HSCT depending on HBV serology.
    - CMV reactivation management: Consider cytomegalovirus (CMV) monitoring and pre-emptive therapy (eg, IV ganciclovir, IV foscarnet or oral valganciclovir) for all patients; for patients undergoing allogeneic HSCT, CMV monitoring and pre-emptive therapy strongly recommended until at least 6 months after transplantation.
    - Antifungal prophylaxis: Consider prophylaxis with fluconazole or amphotericin B agent for all patients treated with chemotherapy; for patients undergoing allogeneic HSCT, antifungal prophylaxis with fluconazole or micafungin strongly recommended until at least day 75 after transplantation.
    - Pneumocystis pneumonia (PCP) prophylaxis: trimethoprim-sulfamethoxazole (TMP-SMX)<sup>1</sup>
  - ◆ Heightened awareness for risk of sepsis/death due to steroid therapy and neutropenia
  - ◆ Febrile neutropenia management
    - Fever is defined as a single temperature  $\geq 38.3$  °C (101°F) or  $\geq 38.0$  °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 Guidelines)
- Pegaspargase Toxicity Management - see [ALL-B 3 of 4](#) and [ALL-B 3 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.

[Continued on ALL-B 2 of 4](#)

<sup>1</sup>There may be important drug interactions with methotrexate that need to be considered prior to initiation of methotrexate-based therapy.

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**SUPPORTIVE CARE (2 of 4)**

- **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)<sup>1</sup> is recommended during steroid therapy
  - ◆ **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
- **Transfusions**
  - ◆ Products should be irradiated
- **Use of filgrastim (granulocyte colony-stimulating factor [G-CSF])**
  - ◆ 5 mcg/kg/day subcutaneously (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](#))
- **Antiemetics ([See NCCN Guidelines for Antiemesis](#))**
  - ◆ 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](#))**

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**SUPPORTIVE CARE (3 of 4)**

**Pegaspargase Toxicity Management**

Toxicity	CTCAE Toxicity Grade		
	1	2	3 and 4
<b>Systemic Allergic Reaction/ Anaphylaxis</b>	<b>Permanently discontinue pegaspargase; substitute asparaginase Erwinia chrysanthemi.</b>		
<b>Pancreatitis</b>	<b>Continue pegaspargase for asymptomatic amylase or lipase elevation &gt; 3.0 x ULN (chemical pancreatitis) or only radiologic abnormalities; observe closely for rising amylase or lipase levels. Continue pegaspargase for non-symptomatic chemical pancreatitis but observe patient closely for development of symptomatic pancreatitis for early treatment.</b>		<b>Permanently discontinue all pegaspargase for clinical pancreatitis (vomiting, severe abdominal pain) with amylase or lipase elevation &gt; 3 x ULN for &gt; 3 days and/or development of pancreatic pseudocyst.</b>
<b>Hepatic transferasemia</b>	<b>For alanine or glutamine aminotransferase elevation &gt; 3.0 - 5.0 x ULN, continue pegaspargase.</b>	<b>For alanine or glutamine aminotransferase elevation &gt; 5.0 - 20.0 x ULN, delay next dose of pegaspargase until grade &lt; 2.</b>	<b>For alanine or glutamine aminotransferase elevation &gt; 20.0 x ULN, discontinue pegaspargase if toxicity reduction to grade &lt; 2 takes &gt; 1 week.</b>
<b>Hyper-bilirubinemia</b>	<b>Continue pegaspargase if direct bilirubin &lt; 3.0 mg/dL.</b>	<b>If direct bilirubin 3.1 - 5.0 mg/dL, hold pegaspargase and resume when direct bilirubin is &lt; 2.0 mg/dL.</b>	

Adapted from Stock W, Douer D, DeAngelo DJ, et al. Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. *Leuk Lymphoma* 2011;52:2237-2253.

National Cancer Institute; National Institute of Health. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 2010. Available at: [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_8.5x11.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Accessed February 2013.

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### SUPPORTIVE CARE (4 of 4)

#### Pegaspargase Toxicity Management

Toxicity	CTCAE Toxicity Grade		
	1	2	3 and 4
<b>Non-CNS thrombosis</b>	For abnormal laboratory findings without clinical correlates, continue pegaspargase.	Withhold pegaspargase until acute toxicity and clinical signs resolve and anticoagulant therapy stable or completed; do not withhold pegaspargase for abnormal laboratory findings without a clinical correlate.	
<b>Non-CNS hemorrhage</b>	Do not withhold pegaspargase for abnormal laboratory findings without a clinical correlate.	For bleeding in conjunction with hypofibrinogenemia, withhold pegaspargase until bleeding $\leq$ grade 1, until acute toxicity and clinical signs resolve, and coagulant replacement therapy stable or completed.	
<b>CNS thrombosis</b>	For abnormal laboratory findings without a clinical correlate, continue pegaspargase.	Discontinue all pegaspargase; if CNS symptoms and signs are fully resolved and significant pegaspargase remains to be administered, may resume pegaspargase therapy at a lower dose and/or longer intervals between doses with closely monitored anticoagulation.	Permanently discontinue all pegaspargase.
<b>CNS hemorrhage</b>	Discontinue all pegaspargase; if CNS symptoms and signs are fully resolved and significant pegaspargase remains to be administered, may resume pegaspargase therapy at a lower dose and/or longer intervals between doses.		Permanently discontinue all pegaspargase.

Adapted from Stock W, Douer D, DeAngelo DJ, et al. Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. *Leuk Lymphoma* 2011;52:2237-2253.

National Cancer Institute; National Institute of Health. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 2010. Available at: [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_8.5x11.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Accessed February 2013.

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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.<sup>1,2</sup>
- 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% to 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.
- 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, which is typically done concurrently with the first cycle of maintenance chemotherapy.

<sup>1</sup>Gokbuget N, Hoelzer D. Treatment of adult acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2006:133-141;

<sup>2</sup>Lazarus HM, Richards SM, Chopra R, et al. Central nervous system involvement in adult acute lymphoblastic leukemia at diagnosis: results from the international ALL trial MRC UKALL XII/ECOG E2993. Blood 2006;108:465-472.

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### PRINCIPLES OF CHEMOTHERAPY (1 of 4)

#### Induction Regimens<sup>a</sup> 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<sup>1-4</sup>
- TKIs + multiagent chemotherapy: imatinib; and daunorubicin, vincristine, prednisone, and cyclophosphamide<sup>5,6</sup>
- TKIs (imatinib or dasatinib)<sup>7,8,9</sup> + corticosteroids
- TKIs + vincristine + dexamethasone<sup>10,11</sup>

##### 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<sup>12</sup>
- TKIs + hyper-CVAD: imatinib or dasatinib; and hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate, and cytarabine<sup>1-4</sup>
- TKIs + multiagent chemotherapy: imatinib; and daunorubicin, vincristine, prednisone, and cyclophosphamide<sup>5,6</sup>

##### 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<sup>b,c</sup>

[Induction Regimens for Ph-Negative \(ALL ALL-D 2 of 4\)](#)

[Regimens for Relapsed/Refractory ALL ALL-D 3 of 4](#)

[References ALL-D 4 of 4](#)

<sup>a</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>b</sup>For patients receiving 6-MP, consider testing for TPMT gene polymorphisms, particularly in patients that develop severe neutropenia after starting 6-MP.

<sup>c</sup>Dose modifications for antimetabolites in maintenance should be consistent with the chosen treatment regimen. It may be necessary to reduce dose/eliminate antimetabolite in the setting of myelosuppression and/or hepatotoxicity.

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PRINCIPLES OF CHEMOTHERAPY (2 of 4)

**Induction Regimens<sup>a</sup> 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<sup>13</sup>
- Linker 4-drug regimen: daunorubicin, vincristine, prednisone, and pegaspargase<sup>14</sup>
- 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<sup>15,16</sup>
- MRC UKALLXII/ECOG2993 regimen: daunorubicin, vincristine, prednisone, and pegaspargase (induction phase I); and cyclophosphamide, cytarabine, and 6-mercaptopurine<sup>b</sup> (induction phase II)<sup>17</sup>

**Pediatric-inspired protocols for AYA patients aged 15-39 years:**

- GRAALL-2003 regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide (patients aged <60 years)<sup>18</sup>
- COG AALL-0434 regimen with nelarabine (for T-ALL): daunorubicin, vincristine, prednisone, and pegaspargase; nelarabine added to consolidation regimen (ongoing study)<sup>19</sup>
- CCG-1961 regimen: daunorubicin, vincristine, prednisone, and pegaspargase (patients aged ≤21 years)<sup>20,21</sup>
- PETHEMA ALL-96 regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide (patients aged <30 years)<sup>22</sup>
- 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)<sup>23</sup>

**Maintenance regimen:**

- Weekly methotrexate + daily 6-mercaptopurine<sup>b</sup> + monthly vincristine/prednisone pulses (for 2-3 years)

[Induction Regimens for Ph-Positive ALL \(ALL-D 1 of 4\)](#)

[Regimens for Relapsed/Refractory ALL \(ALL-D 3 of 4\)](#)

[References \(ALL-D 4 of 4\)](#)

<sup>a</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>b</sup>For patients receiving 6-MP, consider testing for TPMT gene polymorphisms, particularly in patients that develop severe neutropenia after starting 6-MP.

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PRINCIPLES OF CHEMOTHERAPY (3 of 4)

**Regimens<sup>d</sup> for Relapsed/Refractory ALL**

**Ph-positive ALL:**

- Dasatinib<sup>24,25,e</sup>
- Nilotinib<sup>26,f</sup>
- Bosutinib<sup>27,g</sup>
- Ponatinib<sup>28,h</sup>

**Ph-negative ALL:**

- Clofarabine-containing regimens<sup>29,30</sup>
- Cytarabine-containing regimens<sup>31</sup>
- Alkylator combination regimens<sup>32</sup>
- Nelarabine (for T-ALL)<sup>33</sup>
- Augmented hyper-CVAD: hyper-fractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, and pegaspargase; alternating with high-dose methotrexate and cytarabine<sup>34</sup>
- Vincristine sulfate liposome injection (VSLI)<sup>35,36</sup>

[Induction Regimens for Ph-Positive \(ALL ALL-D 1 of 4\)](#)

[Induction Regimens for Ph-Negative \(ALL ALL-D 2 of 4\)](#)

[References \(ALL-D 4 of 4\)](#)

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

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

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

<sup>h</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 (e.g. 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/2013/203469s007s008lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203469s007s008lbl.pdf).

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## PRINCIPLES OF CHEMOTHERAPY (4 of 4) - References

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### RESPONSE CRITERIA

#### Response Criteria for Blood and Bone Marrow:

- CR
  - ◆ No circulating blasts or extramedullary disease
    - No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement
  - ◆ Trilineage hematopoiesis (TLH) and <5% blasts
  - ◆ Absolute neutrophil count (ANC) >1000/microL
  - ◆ Platelets >100,000/microL
  - ◆ No recurrence for 4 weeks
- CR with incomplete blood count recovery (CRi)
  - ◆ Recovery of platelets but <100,000 or ANC is <1000/microL
- Overall response rate (ORR=CR + CRi)
- Refractory disease
  - ◆ Failure to achieve CR at the end of induction
- Progressive disease (PD)
  - ◆ Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
- Relapsed disease
  - ◆ Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after a CR

#### Response Criteria for CNS Disease:

- CNS remission: Achievement of CNS-1 status ([see ALL-C](#)) in a patient with CNS-2 or CNS-3 status at diagnosis.
- CNS relapse: New development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome.

#### Response Criteria for Mediastinal Disease:

- CR: Complete resolution of mediastinal enlargement by CT.
- CR Unconfirmed (CRu): Residual mediastinal enlargement that has regressed by >75% in the sum of the product of the greatest perpendicular diameters (SPD).
- PR: >50% decrease in the SPD of the mediastinal enlargement.
- PD: >25% increase in the SPD of the mediastinal enlargement.
- No Response (NR): Failure to qualify for PR or PD.
- Relapse: Recurrence of mediastinal enlargement after achieving CR or CRu.

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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 most frequently employed methods for MRD assessment include multicolor flow cytometry to detect abnormal immunophenotypes and real-time quantitative polymerase chain reaction (RQ-PCR) assays to detect fusion genes (eg, *BCR-ABL1*), clonal rearrangements in immunoglobulin (Ig) heavy chain genes, and/or T-cell receptor (TCR) genes.
- Current multicolor flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of  $<1 \times 10^{-4}$  ( $<0.01\%$ ) bone marrow mononuclear cells (MNCs).<sup>1,2</sup> 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  $1 \times 10^6$  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  $1 \times 10^7$  MNCs for initial marker characterization and generation of individual dilution series;  $1 \times 10^6$  MNCs are sufficient for follow-up analysis.
  - ◆ The minimal limit of assay sensitivity (to declare MRD negativity) should be  $<1 \times 10^{-4}$  ( $<0.01\%$ ).
- 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 (eg, 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.<sup>1</sup> 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 reference laboratories with expertise in MRD assays; note that results from one lab to another may not be directly equivalent or comparable

<sup>1</sup>Bruggemann M, Schrauder A, Raff T, et al. Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18-20 September 2008. *Leukemia* 2010;24:521-535;

<sup>2</sup>Campana D. Minimal residual disease in acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program* 2010;2010:7-12.

**Note:** All recommendations are category 2A unless otherwise indicated.

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



## Discussion

### 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.**

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## Overview

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia (ALL) were developed as a result of meetings convened by a multidisciplinary panel of ALL experts, with the goal of providing recommendations on standard treatment approaches based on current evidence. The NCCN Guidelines and the following discussions focus on the classification of ALL subtypes based on immunophenotype and cytogenetic/molecular markers;; risk assessment and stratification for risk-adapted therapy; treatment strategies for Philadelphia chromosome (Ph)–positive and Ph-negative ALL for both adolescents 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.

ALL is a heterogenous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs.<sup>1</sup> The age-adjusted incidence rate of ALL in the United States is 1.7 per 100,000 individuals per year, with approximately 6020 new cases and 1440 deaths estimated in 2014.<sup>2</sup> The median age at diagnosis for ALL is 14 years with 60% of patients diagnosed at younger than 20 years. In contrast, 24% are cases are diagnosed at 45 years or older<sup>2</sup> and only approximately 11% of patients are diagnosed at 65 years or older.<sup>3</sup> 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.<sup>1,4</sup>

Risk factors for developing ALL include older age (>70 years), exposure to chemotherapy or radiation therapy, and genetic disorders,

particularly Down syndrome.<sup>5,6</sup> Although rare, other genetic conditions have been categorized as a risk factor for ALL and include neurofibromatosis,<sup>7</sup> Klinefelter syndrome,<sup>8-10</sup> Fanconi anemia,<sup>11,12</sup> Shwachman syndrome,<sup>13,14</sup> Bloom syndrome<sup>15</sup> and ataxia telangiectasia.<sup>16</sup>

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 has shown a 5-year overall survival (OS) of 86-89% for children;<sup>17,18</sup> 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 of 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.<sup>19</sup> Although the exact OS percentage can vary based on how the age range is defined for pediatric, AYA and adult patients, the trend is none the less clear that OS decreases substantially with increased age. The exception is infants under the age of 1 which have not seen any improvement in survival over the last 30 years. The 5-year OS in the population remains below 60%.<sup>19</sup> (See discussion section Cytogenetic and Molecular Subtypes) Cure rates for AYAs with ALL remain suboptimal compared with those for children, although these outcomes represent substantial improvements with the recent adoption of pediatric treatment regimens.<sup>20</sup> 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 *TEL-AML1* 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 nonspecific, and may include fatigue or lethargy, constitutional symptoms (fevers, night sweats, weight loss), dyspnea, dizziness, infections, and easy bruising or bleeding.<sup>1,21</sup> Among children, pain in the extremities or joints may be the only presenting symptom.<sup>1</sup> 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 resulting from cranial nerve involvement, are more suggestive of mature B-cell ALL.<sup>1,21</sup>

The diagnosis of ALL generally requires demonstration of 20% or greater bone marrow lymphoblasts on hematopathology review of bone marrow aspirate and biopsy materials. The 2008 WHO classification lists ALL and lymphoblastic lymphoma as the same entity, distinguished only by the primary location of the disease.<sup>22,23</sup> 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.<sup>22,23</sup> Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens.

Hematopathology evaluations should include morphologic examination of malignant lymphocytes using Wright-Giemsa–stained slides and hematoxylin and eosin (H&E)–stained core biopsy and clot sections; comprehensive immunophenotyping with flow cytometry (see

*Immunophenotyping*); 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*). Subtypes of B-cell ALL with recurrent genetic abnormalities include the following: hyperdiploidy (DNA index >1.16; 51–65 chromosomes); hypodiploidy (<46 chromosomes); t(9;22)(q34;q11.2), *BCR-ABL1*; t(v;11q23), *MLL* rearrangement; t(12;21)(p13;q22), *TEL-AML1*; t(1;19)(q23;p13.3), *E2A-PBX1*; and t(5;14)(q31;q32), *IL3-IGH*.<sup>24</sup> 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 the use of flow cytometry to determine the presence of cell surface antigens on lymphocytes. ALL can be classified broadly into 3 groups based on immunophenotype, which include precursor-B-cell ALL, mature B-cell ALL, and T-cell ALL.<sup>1,25</sup> Among children, B-cell lineage ALL constitutes approximately 88% of cases;<sup>26</sup> in adult patients, subtypes of B-cell lineage ALL constitute approximately 75% of cases (including mature B-cell ALL constituting 5% of adult ALL), whereas the remaining 25% constitute T-cell lineage ALL.<sup>26,27</sup> Within the B-cell lineage, the profile of cell surface markers differs according to different stages 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 referred to as *common ALL antigen*) or surface immunoglobulins. Pre-B-cell ALL is characterized by the presence of cytoplasmic

immunoglobulins and CD10/CD19/CD22/CD79a expression.<sup>1,21,22,27</sup> Pre-B-cell ALL was previously been 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.<sup>1</sup> In addition, 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.<sup>28,29</sup>

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.<sup>1,21,23</sup> Additionally, CD52 may be expressed in 30% to 50% of T-cell lineage ALL in adults.<sup>1</sup> Combined data from the GMALL 06/99 study and the GMALL 07/03 study revealed a distribution of T-cell lineage ALL among three subgroups: cortical/thymic (56%), medullary/mature (21%) and early (23%) T-cell ALL.<sup>25</sup> 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 *Typical Immunophenotype By Major ALL Subtypes* on page ALL-A).

ETP ALL represents a distinct biologic subtype of T-cell lineage ALL that accounts for 12% of pediatric T-ALLs, 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 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.<sup>30</sup> A pivotal study from Zhang et al,<sup>31</sup> 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 encode hematopoietic developmental transcription factors, including GATA3,

ETV6, RUNX1, IKZF1, and EP300, were observed. These mutations are more frequent in myeloid neoplasms than in the other subtypes of ALL suggesting that myeloid-derived therapies and targeted therapy may be better treatment options for select subtypes of ALL.

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 express 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.<sup>22,23</sup> 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.

### 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 differ between adult and childhood ALL, which partially explains the difference in clinical outcomes between 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 to 7% in the adult ALL patient population.<sup>26,32</sup> The *TEL-AML1* subtype (also within the B-cell lineage) resulting from chromosomal

translocation t(12;21) is among the most commonly occurring subtypes (22%) in childhood ALL compared to adults (2%).<sup>26</sup> Both hyperdiploidy and *TEL-AML1* subtypes are associated with favorable outcomes in ALL.<sup>32-34</sup> Ph-positive ALL, associated with poor prognosis, is relatively uncommon among childhood ALL (3%), whereas this abnormality is the most common subtype among adults (25%).<sup>26</sup> The frequency of Ph-positive ALL increases with age (eg, 10% in patients 15–39 years; 25% in patients 40–49 years; 20%–40% in patients >50 years of age).<sup>33,35-37</sup> Moreover, younger children (1–9 years of age) with Ph-positive ALL have a better prognosis than adolescents with this subtype.<sup>38</sup>

Philadelphia-like (Ph-like) ALL is a subgroup of B-cell lineage ALL associated with unfavorable prognosis.<sup>39,40</sup> Similarly to Ph-positive ALL, the 5-year disease free survival in this population is estimated to be 60%,<sup>39</sup> however this phenotype is 4 to 5 times more frequent 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 *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 *ABL1*, *EPOR*, *JAK2*, *PDGFRβ*, *EBF1*, *FLT2*, *IL7R* and *SH2B3* genes.<sup>39-41</sup> Therefore, use of the *ABL1* tyrosine kinase inhibitor 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 *MLL* gene [in particular, cases with t(4;11) translocation] are known to have poor prognosis.<sup>20,28</sup> Hypodiploidy is also associated with poor prognosis and is observed in 1% to 2% of patients.<sup>20,42</sup> 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 (eg, 1%–3% in patients 15–29 years; 3%–6% in patients 30–59 years; 5%–11% in patients >60 years of age).<sup>33</sup>

**Table 1. Common Chromosomal and Molecular Abnormalities in Acute Lymphoblastic Leukemia**

Cytogenetics	Gene	Frequency in Adults	Frequency in Children
Hyperdiploidy (>50 chromosomes)	--	7%	25%
Hypodiploidy (<44 chromosomes)	--	2%	1%
t(9;22)(q34;q11): Philadelphia chromosome (Ph)	<i>BCR-ABL1</i>	25%	2-4%
t(12;21)(p13;q22)	<i>TEL-AML1 (ETV6-RUNX1)</i>	2%	22%
t(v;11q23) [e.g., t(4;11), t(9;11)], t(11;19)	<i>MLL</i>	10%	8%
t(1;19)(q23;p13)	<i>E2A-PBX1 (TCF3-PBX1)</i>	3%	6%
t(5;14)(q31;q32)	<i>IL3-IGH</i>	<1%	<1%
t(8;14), t(2;8), t(8;22)	<i>c-MYC</i>	4%	2%
t(1;14)(p32;q11)	<i>TAL-1<sup>a</sup></i>	12%	7%
t(10;14)(q24;q11)	<i>HOX11 (TLX1)<sup>a</sup></i>	8%	1%
t(5;14)(q35;q32)	<i>HOX11L2<sup>a</sup></i>	1%	3%
t(11;14)(q11) [eg, (p13;q11), (p15;q11)]	<i>TCRα and TCRδ</i>	20%-25%	10%-20%
BCR-ABL1-like	<i>various<sup>b</sup></i>	10%-30%	15%

<sup>a</sup>Abnormalities observed exclusively in T-cell lineage ALL; all others occur exclusively or predominantly in B-cell lineage ALL. <sup>b</sup>See text for more details.

## Workup

The initial workup for patients with ALL should include a thorough medical history and physical examination, along with laboratory and imaging studies (where applicable). Laboratory studies include a CBC count with platelets and differential, a blood chemistry profile, a disseminated intravascular coagulation panel (that includes measurements for D-dimer, fibrinogen, prothrombin time, and partial thromboplastin time), and a tumor lysis syndrome (TLS) panel (that includes measurements for serum lactate dehydrogenase, uric acid, potassium, phosphates, and calcium). Procurement of cells should be considered for purposes of future research (in accordance with

institutional practices or policies). All male patients should be evaluated for testicular involvement of disease; testicular involvement is especially common in cases of T-cell ALL. For patients with T-cell ALL, CT scans of the chest are warranted. All patients should be evaluated for infections, including screening for active infections if febrile or for symptomatic opportunistic infections. Empiric antiinfective therapy should be initiated, as appropriate (see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections; to view the most recent version of these guidelines, visit [NCCN.org](http://NCCN.org)). In addition, an echocardiogram or cardiac scan should be considered for all patients due to the use of anthracyclines as the backbone of nearly all treatment regimens. Assessment of cardiac function is particularly important for patients with prior cardiac history, prior anthracycline exposure, or clinical symptoms suggestive of cardiac dysfunction, and for elderly patients. Except in patients with major contraindications to hematopoietic stem cell transplantation (HSCT), HLA typing should be performed at workup. In patients with poor-risk features who lack a sibling donor, an early evaluation and search for alternative donors should be considered.

Appropriate imaging studies (eg, CT/MRI scan of the head) should be performed to detect meningeal disease, choroidomas, or central nervous system (CNS) bleeding for patients with major neurologic signs or symptoms at diagnosis. CNS involvement should be evaluated through lumbar puncture at timing that is consistent with the treatment protocol. Pediatric-inspired regimens typically include lumbar puncture at diagnostic workup; however, the NCCN ALL Panel recommends that lumbar puncture, if performed, be done concomitantly with initial intrathecal therapy (see *NCCN Recommendations for Evaluation and Treatment of Extramedullary Involvement*).

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

### **Prognostic Factors and Risk Stratification**

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

#### **Prognostic Factors in AYA Patients With ALL**

Initially, risk assessment for childhood ALL was individually determined by the institution, complicating the interpretation of data. However, in 1993, a common set of risk criteria was established by the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG) at an international conference hosted by the National Cancer Institute.<sup>43</sup> In this system, two risk groups were designated: standard risk and high risk. Standard risk was assigned in patients aged 1 to less than 10 years of age and with a WBC count less than  $50 \times 10^9$  cells/L, whereas all other patients with ALL, including T-cell ALL (regardless of age or WBC count), were considered high risk.<sup>42</sup> It should be noted that despite exclusion from this report, patients under age 1 year should also be considered very high risk. The POG and CCG have since merged to form the Children's Oncology Group (COG) and subsequent risk assessment strategy has produced additional risk factors, particularly in precursor B-cell ALL, to further refine therapy. Specifically, in B-cell ALL, a group identified as very high risk was defined as patients with any of the following characteristics: t(9;22) chromosomal translocation (ie, Ph-positive ALL) and/or presence of BCR-ABL fusion protein; hypodiploidy (<44 chromosomes) or a DNA

index below 0.81;<sup>44</sup> or failure to achieve remission with induction therapy.<sup>20,42</sup> MLL rearrangements and a poor response to induction chemotherapy also re-categorized patients into this group.<sup>45-47</sup>

Conversely, criteria were refined for lower risk and included patients with hyperploidy, the t(12;21) chromosomal translocation (*TEL-AML1* subtype),<sup>48</sup> or simultaneous trisomies of chromosomes 4, 10, and 17.<sup>42,49</sup> Presence of extramedullary disease and the early response to treatment also modified risk. Early marrow response to therapy was a strong positive prognostic factor while the presence of extramedullary disease at diagnosis was correlated with a poorer prognosis. Using the refined risk assessment, four risk categories for B-cell ALL, designated as low risk, standard risk, high risk and very high risk were identified encompassing 27%, 32%, 27% and 4% of cases, respectively.<sup>42</sup>

Risk stratification of T-cell ALL has been more difficult than in B-cell ALL. Although T-cell ALL is often categorized as very high risk depending on the institute, newer treatment options have resulted in improved survival outcomes for these patients. Furthermore, the identification of genetic mutations and the use of targeted therapies may change the way T-cell ALL is treated and ultimately how these patients are assessed for risk.

Variability exists across studies with regard to the age ranges defined for AYA patients. The NCI defines the age range for AYA patients as 15 to 39 years. This definition has been adopted for the AYA sections of the NCCN Guidelines for ALL. Historically, the AYA population has been treated on either a pediatric or an adult ALL regimen, depending on referral patterns and the institution. However, studies in the past have shown poorer outcomes among patients in the AYA group compared with children younger than 10 years.<sup>50</sup> This may be attributed to factors that are based on biology and social differences. Compared to the pediatric population, AYA patients have a lower frequency of

favorable chromosomal/cytogenetic abnormalities, such as hyperdiploidy or *TEL-AML1*<sup>51</sup> and a greater incidence of poor risk cytogenetics including Ph-positive ALL, hypodiploidy and complex karyotype<sup>52</sup> and a higher incidence of early T precursor ALL.<sup>30,53</sup> Furthermore, the positive prognostic values of the *TEL-AML1* mutation and hyperdiploidy are greater in the pediatric population suggesting that the benefits decline with age.<sup>52</sup> The effects of the treatment are also shown to be different in the AYA population compared to the pediatric population. In vitro studies showed that ALL cells from children over 10 years of age are more resistant to chemotherapy compared to the cells from children younger than 10 years.<sup>54</sup> This observation has extended into clinical trials where an inferior response to chemotherapy is observed.<sup>55</sup> In addition to the biological differences, the social component of treating AYA patients is important. Enrollment in clinical trials has been shown to improve patient outcomes;<sup>56</sup> however, only 2% of AYA patients enroll in clinical trials compared to the 60% enrollment of pediatric patients.<sup>57</sup> Pediatric patients have also been shown to be more compliant to treatment protocols compared to AYA patients<sup>58</sup> which may be due to greater parental supervision of the treatment and better insurance.<sup>59</sup>

In recent years, several retrospective studies from both the United States and Europe have shown that AYA patients (15–21 years of age) treated on a pediatric protocol have substantially improved EFS outcomes than same-aged patients treated on adult ALL regimens.<sup>20,34</sup> Comparison of adult and pediatric protocols have shown that adults received lower doses of nonmyelosuppressive chemotherapy and less intense intrathecal chemotherapy regimens.<sup>60,61</sup> Adult protocols also entail a greater use of allogeneic stem cell transplantation compared to pediatric protocols but the benefits of HSCT in the AYA population has not been sufficiently studied and the available data have conflicting

findings.<sup>62-66</sup> However, this is a significant difference between the way adults and pediatric patients are treated and may be a variable in the treatment of AYA patients. Thus, the choice of initial treatment regimen can have a profound impact on overall clinical outcomes in AYA patients.

### Prognostic Factors in Adults With ALL

Both age and initial WBC count have historically been considered clinically significant prognostic factors in the management of adult patients with ALL.<sup>25,28</sup> Early prospective multicenter studies defined values for older age (>35 years) and higher initial WBC count (>30 × 10<sup>9</sup>/L) that were predictive of significantly decreased remission duration.<sup>67,68</sup> Subsequent studies have confirmed the prognostic importance of these clinical parameters, although the cutoff values differed between studies.<sup>25,28</sup>

In one of the largest studies to date (n = 1521) conducted by the Medical Research Council (MRC) UKALL/ECOG, both age (>35 years) and WBC count (>30 × 10<sup>9</sup>/L for B-cell lineage; >100 × 10<sup>9</sup>/L for T-cell lineage) were found to be significant independent prognostic factors for decreased disease-free survival (DFS) and overall survival (OS) among patients with Ph-negative ALL; the independent prognostic value remained significant when these factors were evaluated as continuous variables in multivariate analysis.<sup>69</sup> All patients, regardless of Ph status, had received induction therapy followed by intensification (for patients with a complete remission [CR] postinduction) with contemporary chemotherapy combination regimens. Patients with a CR after induction received allogeneic HSCT (for patients <50 years old and with HLA-compatible siblings), autologous HSCT, or consolidation/maintenance treatment. Because Ph-positive ALL is associated with a very poor prognosis, patients with this subtype were assigned to undergo

allogeneic HSCT (including matched unrelated donor HSCT), when possible. The 5-year OS rate among patients with Ph-positive and Ph-negative disease was 25% and 41%, respectively.<sup>69</sup> Among the patients with Ph-negative ALL, those older than 35 years or with elevated WBC count ( $>30 \times 10^9/L$  for B-cell lineage;  $>100 \times 10^9/L$  for T-cell lineage) at diagnosis were initially identified as high risk, whereas all others were classified as standard risk. The 5-year OS rates for the Ph-negative high-risk and standard-risk subgroups were 29% and 54%, respectively.<sup>69</sup> Further analysis of the Ph-negative population according to risk factors showed that patients could be categorized as low risk (no risk factors based on age or WBC count), intermediate risk (either age  $>35$  years or elevated WBC count), or high risk (both age  $>35$  years and elevated WBC count). The 5-year OS rates based on these risk categories were 55%, 34%, and 5%, respectively, suggesting that patients with Ph-negative ALL in the high-risk subgroup had even poorer survival outcomes than patients in the overall Ph-positive subgroup.<sup>69</sup>

In a subsequent analysis from this MRC UKALL XII/ECOG 2993 study, cytogenetic data were evaluated in approximately 1000 patients.<sup>70</sup> The analysis confirmed the negative prognostic impact of Ph-positive status compared with Ph-negative disease, with a significantly decreased 5-year EFS rate (16% vs. 36%;  $P < .001$ , adjusted for age, gender, and WBC count) and OS rate (22% vs. 41%;  $P < 0.001$ , adjusted for age, gender, and WBC count). Among patients with Ph-negative disease, the following cytogenetic subgroups had significantly decreased 5-year EFS (13%–24%) and OS rates (13%–28%) based on univariate analysis:  $t(4;11)$  *MLL* translocation,  $t(8;14)$ , complex karyotype ( $\geq 5$  chromosomal abnormalities) and low hypodiploidy (30–39 chromosomes)/near triploidy (60–78 chromosomes).<sup>70</sup> In contrast,  $del(9p)$  or high hyperdiploidy (51–65 chromosomes) was associated

with more favorable 5-year EFS (49%–50%) and OS rates (53%–58%).<sup>70</sup> An earlier report of data from patients treated on the French ALL study group (LALA) protocols suggested that near triploidy (60–78 chromosomes) may be derived from duplication of hypodiploidy (30–39 chromosomes); both aneuploidies were associated with poor DFS and OS outcomes similar to that of patients with Ph-positive ALL.<sup>71</sup> Based on multivariate Cox regression analysis reported in the MRC UKALL XII/ECOG 2993 study,  $t(8;14)$ , low hypodiploidy/near triploidy, and complex karyotype remained significant independent predictors for risk of relapse or death; the prognostic impact of these cytogenetic markers was independent of factors such as age, WBC count, or T-cell immunophenotype, and their significance was retained even after excluding patients who had undergone postinduction HSCT.<sup>70</sup>

The importance of cytogenetics as a prognostic factor for survival outcomes was shown in other studies, including the Southwest Oncology Group (SWOG) study conducted in 200 adult patients with ALL.<sup>72</sup> In this study, the prognostic impact of the different cytogenetic categories outweighed that of the more traditional factors, such as age and WBC count; in multivariate analysis for both relapse-free survival (RFS) and OS, cytogenetics remained a significant independent predictor of outcomes, whereas factors such as age and WBC count lost prognostic significance.<sup>72</sup> Moreover, the subgroup ( $n = 19$ ) of patients with “very high risk” cytogenetic features (identified based on outcomes from the MRC/ECOG study mentioned earlier: presence of  $t(4;11)$  *MLL* translocation;  $t(8;14)$ ; complex karyotype; or low hypodiploidy) had substantially decreased 5-year RFS and OS rates (22%, for both end points). Analysis by ploidy status was not possible because only 2 patients were considered to have low hypodiploidy/near triploidy. The 5-year RFS and OS rates among patients with Ph-positive ALL ( $n = 36$ ) were 0% and 8%, respectively.<sup>72</sup>

### NCCN Recommendations for Risk Assessment in ALL

Although some debate remains regarding the risk stratification approach to ALL, the panel suggests the following approaches for defining risk in these patients.

Because AYA patients (defined as age 15–39 years) may benefit from pediatric-inspired ALL treatment protocols, this patient population is considered separately from the adult population (defined as age  $\geq 40$  years). Given the poor prognosis associated with Ph-positive ALL and the wide availability of agents that specifically target the BCR-ABL kinase, initial risk stratification for all patients (AYA or adult) is based on the presence or absence of the t(9;22) chromosomal translocation and/or BCR-ABL fusion protein.

AYA patients with Ph-negative ALL can be further categorized as having high-risk disease, which may be particularly helpful when consolidation with allogeneic HSCT is being considered. High risk is generally defined as having any of the following poor-risk cytogenetic factors: hypodiploidy ( $< 44$  chromosomes); t(v;11q23) or *MLL* rearrangements; t(9;22) or *BCR-ABL* gene mutations; or complex karyotype ( $\geq 5$  chromosomal abnormalities). The absence of all poor-risk factors is considered standard risk. Elevated WBC count ( $\geq 30 \times 10^9/L$  for B-cell lineage;  $\geq 100 \times 10^9/L$  for T-cell lineage) has been considered a high-risk factor in some studies, as discussed above (see sections on Prognostic Factors). Evaluation of WBC count and age for determination of prognosis should ideally be made in the context of treatment protocol-based risk stratification.

For adult patients with ALL (Ph-positive or Ph-negative), these guidelines further stratify patients by age, using 65 years as the cutoff, to guide treatment decisions. However, chronologic age alone is a poor

surrogate for determining patient fitness for therapy. Patients should, therefore, be evaluated on an individual basis.

For adult patients with Ph-negative ALL who are younger than 65 years (or for those with no substantial comorbidities), further risk stratification can be used to categorize patients as having high-risk disease. As with AYA patients, high risk is defined as having any of the following poor-risk cytogenetic factors: hypodiploidy; t(v;11q23) or *MLL* rearrangements; t(9;22) or *BCR-ABL* gene mutations; or complex karyotype ( $\geq 5$  chromosomal abnormalities). The absence of all of the described poor-risk factors is considered standard risk. These additional risk stratification parameters are generally not used for patients aged 65 years or older (or for patients with substantial comorbid conditions) with Ph-negative ALL. Similar to AYA patients, elevated WBC count ( $\geq 30 \times 10^9/L$  for B-cell lineage;  $\geq 100 \times 10^9/L$  for T-cell lineage) has been considered a high-risk factor based on some earlier studies; however, more recent studies in adult patients have demonstrated that WBC counts may lose independent prognostic significance when cytogenetic factors are considered. Data showing the effect of WBC counts on prognosis in adult patients with ALL are less firmly established than in the pediatric population. Therefore, adult patients with ALL may not necessarily be classified as high risk based on high WBC count alone.

### Overview of Treatment Phases in ALL Management

The treatment approach to ALL represents one of the most complex and intensive programs in cancer therapy. Although the specific treatment regimens and selection of drugs, dose schedules, and treatment durations differ between AYA patients and adults, and among different subtypes of ALL, the basic treatment principles are similar. The most common treatment regimens used in patients with ALL

include modifications or variations of multiagent chemotherapy regimens originally developed by the Berlin-Frankfurt-Münster Group (BFM) for pediatric patients (eg, regimens used by COG for children and AYA patients, or the CALGB regimen for adult patients), and the hyper-CVAD regimen (cycles of fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with cycles of high-dose methotrexate and cytarabine) developed at MD Anderson Cancer Center (MDACC). In general, the treatment phases can be largely grouped into induction, consolidation, and maintenance. All treatment regimens for ALL include CNS prophylaxis and/or treatment.

### Induction

The intent of initial induction therapy is to reduce tumor burden by clearing as many leukemic cells as possible from the bone marrow. Induction regimens are typically based on a backbone that includes a combination of vincristine, anthracyclines (eg, daunorubicin, doxorubicin), and corticosteroids (eg, prednisone, dexamethasone) with or without L-asparaginase and/or cyclophosphamide.<sup>1,20,25,28,34</sup> In addition, antimetabolites, such as methotrexate, cytarabine, and/or 6-mercaptopurine (6-MP), are often included at induction therapy, primarily for CNS prophylaxis (see next section).

The BFM/COG regimens are mainly based on a 4-drug induction regimen that includes a combination of vincristine, an anthracycline, a corticosteroid, and L-asparaginase.<sup>73-77</sup> The CALGB regimens are typically based on a 5-drug regimen, which adds cyclophosphamide to the above 4-drug combination.<sup>78</sup> Randomized studies comparing the use of dexamethasone versus prednisone as part of induction therapy in children with ALL showed that dexamethasone significantly decreased the risk of isolated CNS relapse and improved EFS outcomes compared with prednisone.<sup>79,80</sup> The observed advantage in

outcomes with dexamethasone may partly be attributed to improved penetration of dexamethasone in the CNS.<sup>81</sup> In a recently published meta-analysis comparing outcomes with dexamethasone versus prednisone in induction regimens for childhood ALL, dexamethasone was associated with a significantly reduced risk for events (ie, death from any cause, refractory or relapsed leukemia, or second malignancy; risk ratio [RR], 0.80; 95% CI, 0.68–0.94) and CNS relapse (RR, 0.53; 95% CI, 0.44–0.65).<sup>82</sup> However, no advantage was seen with dexamethasone regarding risk for bone marrow relapse (RR, 0.90; 95% CI, 0.69–1.18) or overall mortality (RR, 0.91; 95% CI, 0.76–1.09), and dexamethasone was associated with a significantly higher risk of mortality during induction therapy (RR, 2.31; 95% CI, 1.46–3.66), neuropsychiatric adverse events (RR, 4.55; 95% CI, 2.45–8.46), and myopathy (RR, 7.05; 95% CI, 3.00–16.58) compared with prednisone.<sup>82</sup> Although dexamethasone seems beneficial in terms of reduced risks for CNS relapse and improved EFS, toxicities may be of concern, and an advantage for OS has yet to be conclusively shown.

The hyper-CVAD regimen may be considered a less complex treatment regimen compared with CALGB regimen, and comprises 8 alternating treatment cycles with the “A” regimen (hyper-CVAD: hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and the “B” regimen (high-dose methotrexate and cytarabine).<sup>83-85</sup> CNS prophylaxis and/or CNS-directed treatment (which may include cranial irradiation for patients with CNS leukemia at diagnosis), and maintenance treatment (as discussed in next section) are also used with the hyper-CVAD regimen.

### CNS Prophylaxis and Treatment

The goal of CNS prophylaxis and/or treatment is to prevent CNS disease or relapse by clearing leukemic cells within sites that cannot be

readily accessed with systemic chemotherapy because of the blood-brain barrier. CNS-directed therapy may include cranial irradiation, intrathecal chemotherapy (eg, methotrexate, cytarabine, corticosteroids), and/or high-dose systemic chemotherapy (eg, methotrexate, cytarabine, 6-MP, L-asparaginase).<sup>1,34,81</sup> CNS prophylaxis is typically given to all patients throughout the entire course of ALL therapy, from induction, to consolidation, to the maintenance phases of treatment.

### Consolidation

The intent of postinduction consolidation is to eliminate any leukemic cells potentially remaining after induction therapy, further eradicating residual disease. The postremission induction phase of treatment (but before long-term maintenance therapy) may also be described as *intensification therapy*. The combination of drugs and duration of therapy for consolidation regimens vary largely among studies and patient populations but can comprise combinations of drugs similar to those used during the induction phase. High-dose methotrexate, cytarabine, 6-MP, and L-asparaginase are frequently incorporated into consolidation/intensification regimens, particularly for regimens geared toward children with ALL.<sup>21,25,28,34,76,77</sup>

### Maintenance

The goal of extended maintenance therapy is to prevent disease relapse after postremission induction and consolidation therapy. Most maintenance regimens are based on a backbone of daily 6-MP and weekly methotrexate (typically with the addition of periodic vincristine and corticosteroids) for 2 years in adults and 2 to 3 years in children.<sup>20,25,28,34</sup> Maintenance therapy is omitted for patients with mature B-cell ALL (see the NCCN Guidelines for Non-Hodgkin's Lymphoma: Burkitt Lymphoma; to view the most recent version of these guidelines,

visit NCCN.org), given that long-term remissions are seen early with short courses of intensive therapy in these patients, with relapses rarely occurring beyond 12 months.<sup>25,86</sup>

Factors that affect the bioavailability of 6-MP can significantly impact patient care. Oral 6-MP can have a highly variable drug and metabolite concentrations among patients.<sup>87,88</sup> Furthermore, age, gender, and genetic polymorphisms can affect bioavailability.<sup>89-91</sup> The concomitant use of other chemotherapeutic agents such as methotrexate can also alter toxicity.<sup>92</sup> The efficacy of maintenance therapy is determined by the metabolism of 6-MP to the antimetabolite chemotherapeutic agent 6-thioguanine (6-TGN); however, other pathways compete for 6-MP, thereby reducing the amount of active metabolite produced. The three enzymes that metabolize 6-MP are xanthine oxidase (XO), hypoxanthine phosphoribosyltransferase (HPRT) and thiopurine methyltransferase (TPMT). Because 6-MP is administered orally, it can be converted to the inactive metabolite 6-thiouric acid by XO in the intestinal mucosa and liver. There is little genetic variation in XO<sup>93,94</sup> but diet has been shown to affect absorption of 6-MP.<sup>95,96</sup> 6-MP that is not metabolized by XO, is available for thiol methylation by TPMT to form 6-methyl mercaptopurine or for metabolism by HPRT to form 6-TGN. The balance between metabolism by HPRT is inversely related to the activity of TPMT as demonstrated by the ability of TPMT polymorphism to affect metabolite production.<sup>97</sup> Compared to the wild-type TPMT phenotype, patients that are homozygous TPMT-deficient require a 10- to 15-fold reduction in 6-MP to alleviate hematopoietic toxicity.<sup>98,99</sup> Heterozygosity at the TPMT gene locus occurs in 5-10% of the population and has been shown to have intermediate enzyme activity,<sup>97,100,101</sup> therefore a 10-15% reduction in 6-MP dose is necessary in these patients to prevent toxicity.<sup>102,103</sup> Determination of patient TPMT genotype using genomic DNA is a recommended to optimize 6-MP

dosing, especially in patients that experience myelosuppression at standard doses.<sup>104,105</sup>

Dose reductions may be necessary if patients have genetic polymorphisms and/or hepatotoxicity whereas dose escalation may be necessary in patients that demonstrate myelosuppression. This should be performed in accordance with the protocol being used; generally protocols (including the ECOG/CALGB study) recommend a dose increase by 25% if an ANC greater than 1500 is observed for more than 6 weeks. Outcomes are better in patients who achieve myelosuppression during maintenance compared with patients that have higher neutrophil counts.<sup>58,106</sup> emphasizing the need for optimal dosing of 6-MP

Noncompliance also results in undertreatment and has entered the forefront, particularly in the AYA population. Compliance issues should be addressed for patients without cytopenia. If increasing doses of 6-MP are given during maintenance but no drop in the counts is observed, this may be indicative of noncompliance.<sup>92</sup> Quantification of 6-MP metabolites (6-TGN and 6-MMPN) can be very useful in determining whether lack of myelosuppression is due to non-compliance or hypermetabolism.

### Targeted Agents

During the past decade, the advent of novel agents targeted to specific genetic abnormalities, such as those associated with Ph-positive ALL, or to specific cell surface antigens, has contributed to improvements in outcomes in some subtypes of ALL. These agents include BCR-ABL selective tyrosine kinase inhibitors (TKIs) for Ph-positive ALL,<sup>107-117</sup> and anti-CD20 monoclonal antibody (eg, rituximab) for CD20-expressing B-cell lineage ALL (especially for mature B-cell ALL).<sup>118,119</sup> In addition, nelarabine has been approved for the treatment of relapsed/refractory

T-cell lineage ALL.<sup>120-122</sup> These agents may be incorporated as part of frontline induction, consolidation, and/or maintenance regimens during the course of initial ALL therapy, and in relapsed/refractory disease settings. Single agent TKI treatment in Ph-positive ALL has demonstrated improved response to induction over chemotherapy but both imatinib<sup>112</sup> and dasatinib<sup>111</sup> had a short duration with no remission. TKIs have shown the most benefit when given in concert with corticosteroids. Not only are DFS and OS rates significantly improved but there is a reduction in adverse events making this a possible treatment option for older or less fit patients with Ph-positive ALL (see *Initial Treatment of Adult Patients with Ph-Positive ALL*).<sup>123</sup>

## Management of Ph-Positive ALL

### Initial Treatment in AYA Patients With Ph-Positive ALL

Ph-positive ALL is rare in children with ALL, occurring in only approximately 3% of pediatric cases compared with 25% of adult cases.<sup>26</sup> The frequency of Ph-positive ALL is slightly higher (5%–7% of cases) among AYA patients,<sup>77</sup> although this subtype is still uncommon relative to its incidence in older adults. Historically, children and adolescents with Ph-positive disease had a poorer prognosis compared with patients with Ph-negative B-cell ALL; however, recent improvements in the treatment options are closing this gap. In a retrospective analysis of children with Ph-positive ALL treated between 1986 and 1996 (n = 326) with intensive chemotherapy regimens with or without allogeneic HSCT, the 5-year EFS (calculated from time of diagnosis) and OS rates were 28% and 40%, respectively, for the entire patient cohort.<sup>38</sup> The 7-year EFS and OS rates were 25% and 36%, respectively. Even among the subgroup of patients considered to have a better prognosis (ie, WBC count <50 × 10<sup>9</sup>/L and age <10 years), the 5-year DFS rate (calculated from time of first CR) was only 49%.<sup>38</sup> In the subgroup of patients who underwent allogeneic HSCT with an HLA-

matched related donor ( $n = 38$ ), significantly higher 5-year DFS (65% vs. 25%;  $P < .001$ ) and OS rates (72% vs. 42%;  $P = .002$ ) were observed than in patients who received only chemotherapy; this benefit with HSCT versus chemotherapy alone was not observed with autologous HSCT or with HSCT from matched unrelated donors. This study showed that allogeneic HSCT from a matched related donor offered improvements in outcomes over chemotherapy alone. In a subsequent analysis of outcomes in children with Ph-positive ALL treated more recently (1995–2005) but also without targeted TKIs, the 7-year EFS and OS rates were 32% and 45%, respectively.<sup>124</sup> Outcomes with allogeneic HSCT from either matched related or unrelated donors appeared similar, and HSCT was shown to provide improved disease control over intensive chemotherapy alone.<sup>124</sup> Although this analysis showed improvements in 7-year EFS rates, outcomes remain suboptimal in patients with Ph-positive ALL.

The emergence of targeted therapies for hematologic malignancies, including the treatment of Ph-positive disorders with TKIs, represents an important advancement in ALL therapy. Imatinib mesylate is an inhibitor of BCR-ABL tyrosine kinase and is approved by the FDA for the treatment of adult patients with relapsed or refractory Ph-positive ALL, and the treatment of previously untreated pediatric patients with Ph-positive ALL. In phase II studies in adults with ALL, imatinib has shown efficacy as single-agent therapy in the relapsed/refractory<sup>125</sup> and frontline settings,<sup>112,126</sup> and in combination with chemotherapy regimens during initial induction, consolidation, and/or maintenance.<sup>108,115-117,127-129</sup>

Although allogeneic HSCT has been considered the standard of care for AYA patients with Ph-positive ALL, its role has become less clear with the advent of BCR-ABL–targeted TKIs such as imatinib. Several studies evaluated the role of allogeneic HSCT in the era of imatinib and

whether imatinib-based therapies provided an additional benefit to HSCT.

A single-center retrospective study in children and adolescents with Ph-positive ALL who underwent allogeneic HSCT ( $n = 37$ ; age 1–16 years) compared outcomes between patients who received pre- and/or post-HSCT imatinib ( $n = 13$ ) and those who did not receive imatinib ( $n = 24$ ).<sup>130</sup> The 3-year DFS (62% vs. 53%, respectively) and relapse rates (15% vs. 26%, respectively) were not significantly improved with the use of imatinib. Patients who received HSCT in first CR had significantly improved DFS rates (71% vs. 29%;  $P = .01$ ) and lower relapse rates (16% vs. 36%;  $P = .05$ ) than those who underwent HSCT in second CR or later.<sup>130</sup>

A recent study from the Spanish Cooperative Group compared outcomes of children and adolescents (age 1–15 years) treated with intermediate-dose imatinib combined with intensive chemotherapy followed by allogeneic HSCT ( $n = 16$ ; 94% proceeded to HSCT) versus those of historical controls who did not receive imatinib before allogeneic HSCT ( $n = 27$ ; 63% proceeded to HSCT).<sup>131</sup> The 3-year EFS rate was significantly higher in the imatinib group compared with the historical controls (79% vs. 30%;  $P = .01$ ).

A phase II study at MDACC evaluated imatinib combined with the hyper-CVAD regimen in patients with previously untreated or minimally treated ALL ( $n = 54$ ; median age, 51 years; range, 17–84 years); 14 patients underwent subsequent allogeneic HSCT.<sup>129</sup> The 3-year OS rate with this regimen was 54%. Among the patients aged 40 years or younger ( $n = 16$ ), a strong trend was observed for OS benefit with allogeneic HSCT (3-year OS rate, 90% vs. 33%;  $P = .05$ ).<sup>129</sup>

In a multicenter COG study (AALL-0031) of children and adolescents with high-risk ALL, the group of patients with Ph-positive ALL (n = 92; age 1–21 years) were treated with an intensive chemotherapy regimen combined with imatinib (340 mg/m<sup>2</sup>/d; given during postremission induction therapy and maintenance).<sup>114</sup> Among the cohort (n = 44) who received continuous imatinib exposure (280 consecutive days before maintenance initiation), the 3-year EFS rate was 80.5% (95% CI, 64.5%–89.8%). This outcome compared favorably with that of a historical population of patients with Ph-positive ALL (n = 120) treated on a POG protocol, which showed a 3-year EFS rate of only 35% (*P* < .0001).<sup>114</sup> Moreover, the 3-year EFS rates were similar among the groups of patients who received chemotherapy combined with continuous imatinib (88%; n = 25) or allogeneic HSCT from a related donor (57%; n = 21) or unrelated donor (72%; n = 11). No major toxicities were found to be associated with the addition of imatinib to the intensive chemotherapy regimen.<sup>114</sup>

### Initial Treatment in Adults With Ph-Positive ALL

Historically, treatment outcomes for adult patients with Ph-positive ALL have been extremely poor. Before the era of targeted TKIs, the 3-year OS rate with chemotherapy regimens was generally less than 20%.<sup>115</sup> Allogeneic HSCT, in the pre-imatinib era, resulted in some improvements over chemotherapy alone, with 2-year OS rates of 40% to 50%<sup>132,133</sup> and 3-year OS rates of 36% to 44%.<sup>63,134</sup> In the large international collaborative MRC UKALL XII/ECOG 2993 trial conducted in patients with previously untreated ALL, the subgroup with Ph-positive disease (n = 267; median age, 40 years; range, 15–60 years) was eligible for allogeneic HSCT if they were younger than 50 (in the ECOG 2993 trial) or 55 (in the MRC UKALL XII trial) years and had a matched sibling or matched unrelated donor.<sup>135</sup> Among the Ph-positive patient cohort, postremission treatment included matched sibling allogeneic

HSCT (n = 45), matched unrelated donor allogeneic HSCT (n = 31), and chemotherapy alone (n = 86). The 5-year OS rate according to postremission therapy was 44%, 36%, and 19%, respectively, and the 5-year EFS rate was 41%, 36%, and 9%, respectively.<sup>135</sup> Both the OS and EFS outcomes for patients who underwent allogeneic HSCT (related or unrelated) were significantly improved compared with those who received only chemotherapy. The incidence of transplant-related mortality was 27% with matched sibling allogeneic HSCT and 39% with matched unrelated donor HSCT. An intent-to-treat analysis of patients with a matched sibling donor versus those without a matched sibling donor showed no statistically significant difference in 5-year OS rate (34% vs. 25%, respectively).<sup>135</sup>

The incorporation of imatinib in the treatment regimen for Ph-positive ALL has led to substantial improvements in outcomes over chemotherapy alone.<sup>115,117,129</sup> Numerous phase II studies have evaluated the efficacy of imatinib combined with chemotherapy regimens in patients with previously untreated disease; these studies showed positive results with the combined regimen, particularly when treatment was followed by allogeneic HSCT.<sup>108,115-117,127-129,136</sup>

In the phase II study from GRAALL (GRAAPH-2003), patients with previously untreated Ph-positive ALL (n = 45; median age, 45 years; range, 16–59 years) received imatinib in combination with chemotherapy during either induction or consolidation therapy.<sup>108,128</sup> Patients in CR with a donor received allogeneic HSCT (n = 24), whereas those with CR and good molecular response but without a donor were eligible for autologous HSCT (n = 10). Nine patients did not receive HSCT and were treated with imatinib-based maintenance therapy. The 4-year OS rate did not differ significantly for patients with a sibling donor compared to patients undergoing autologous HSCT (76% vs. 80%); however, patients receiving an allogeneic HSCT from

an unrelated donor had the lowest 4-year survival (11%). The 4-year OS for patients that received only maintenance imatinib was 33%.<sup>128</sup> These data suggest that improved survival with imatinib-based therapy can be further enhanced by the addition of HSCT.

In the subgroup of patients with Ph-positive ALL (n = 94; median age, 47 years; range, 19–66 years) from the Northern Italy Leukemia Group study (NILG-09/00), outcomes were compared between patients who received chemotherapy with imatinib (n = 59) or without imatinib (n = 35), with or without subsequent HSCT (allogeneic or autologous).<sup>136</sup>

The patients who received imatinib (63% of eligible patients underwent allogeneic HSCT) had significantly higher 5-year OS (38% vs. 23%;  $P = .009$ ) and DFS rates (39% vs. 25%;  $P = .005$ ) compared with those who did not receive imatinib (39% of eligible patients underwent allogeneic HSCT).<sup>136</sup> The 5-year OS rates by treatment type were 47% for allogeneic HSCT (n = 45), 67% for autologous HSCT (n = 9), 30% for imatinib without HSCT (n = 15), and 8% for no imatinib and no HSCT (n = 13); the corresponding treatment-related mortality rates were 17%, 0%, 36%, and 23%, respectively. The 5-year relapse rates were 43%, 33%, 87%, and 100%, respectively.<sup>136</sup>

In a phase II study from the Spanish Cooperative Group, patients with Ph-positive ALL (n = 30; median age, 42 years; range, 8–62 years; only 1 patient was <15 years of age) were treated with intensive chemotherapy combined with imatinib, followed by HSCT and imatinib maintenance.<sup>137</sup> Overall, 53% of patients proceeded to allogeneic HSCT and 17% received autologous HSCT. At a median follow up of 4.1 years, the OS and DFS rates were both 30%. The incidence of transplant-related mortality was 27%.<sup>137</sup> Post-transplant maintenance with imatinib was not feasible in most patients, primarily because of transplant-related complications.

Imatinib combined with the hyper-CVAD regimen was evaluated in a phase II study in patients with previously untreated or minimally treated ALL (n = 54; median age, 51 years; range 17–84 years), with 14 patients undergoing subsequent allogeneic HSCT.<sup>129</sup> The 3-year OS rate with this regimen was 54% overall. Among patients aged 60 years or younger, no statistically significant difference was observed in the 3-year OS rate between patients who received HSCT and those who did not (77% vs. 57%). This finding is in contrast to results for younger patients (age ≤40 years) who received HSCT.

Another phase II study from GRAALL (GRAAPH-2005) compared induction therapy with high-dose imatinib (800 mg daily, days 1–28) combined with vincristine and dexamethasone (arm A) versus imatinib (800 mg daily, days 1–14) combined with hyper-CVAD (arm B) in patients younger than 60 years with previously untreated Ph-positive ALL.<sup>138,139</sup> Eligible patients proceeded to HSCT (allogeneic or autologous) after induction/consolidation phases. The primary endpoint was non-inferiority of the less intensive arm A regimen in terms of MRD response ( $BCR-ABL / ABL$  ratio <0.1% by quantitative polymerase chain reaction [PCR]) after induction/consolidation. In an early report from this study (n = 118; n = 83 evaluable; median age 42 years), 52 patients proceeded to HSCT (allogeneic, n = 41; autologous, n = 11). The estimated 2-year OS rate was 62%, with no significant difference between patients who received imatinib with vincristine and dexamethasone and those who received imatinib with hyper-CVAD (68% vs. 54%, respectively).<sup>138</sup> The 2-year DFS rate was 43%, with no significant difference between induction arms (54% vs. 32%, respectively). In an updated analysis from the GRAAPH-2005 study with a median follow up of 40 months (n = 270; n = 265 evaluable; median age 47 years), MRD response rates after induction/consolidation were similar between arm A and arm B (68%

vs. 63.5%); MRD was undetectable in a similar proportion of patients (28% vs. 22%, respectively).<sup>139</sup> The less intensive regimen with high-dose imatinib combined with vincristine and dexamethasone was therefore considered non-inferior to imatinib combined with hyper-CVAD. No significant differences were observed between arm A and arm B in terms of estimated 3-year EFS (46% vs. 38%) or OS (53% vs. 49%) outcomes. Interestingly, among the patients who proceeded to HSCT after MRD response, those who received autologous HSCT showed a trend for improved 3-year RFS (63% vs. 49.5%) and OS (69% vs. 58%) compared with patients who received allogeneic HSCT. This study suggested that outcomes with less intensive chemotherapy regimens (using high-dose imatinib) may offer similar benefits to more intensive imatinib-containing chemotherapy regimens.<sup>139</sup>

In a phase II study from the Japan Adult Leukemia Study Group (ALL-202), patients with Ph-positive ALL (n = 100) were treated with chemotherapy combined with imatinib administered during induction, consolidation, and maintenance phases.<sup>117,134</sup> An early analysis (n = 80; median age, 48 years; range, 15–63 years) reported a 1-year OS rate of 73% among patients who underwent allogeneic HSCT, compared with 85% for those who did not.<sup>117</sup> A subsequent analysis compared outcomes for the subgroup of patients who received allogeneic HSCT at first CR in this study (n = 51; median age, 38 years; range, 15–64 years) versus those for a historical cohort of patients who received allogeneic HSCT without prior imatinib (n = 122).<sup>134</sup> The 3-year OS (65% vs. 44%;  $P = .015$ ) and DFS rates (58% vs. 37%;  $P = .039$ ) were significantly higher among patients treated with imatinib compared with the historical cohort; the 3-year nonrelapse mortality rate was similar between cohorts (21% vs. 28%, respectively).<sup>134</sup>

Collectively, these studies suggest that incorporation of imatinib into the therapeutic regimen improves outcomes for adult patients with Ph-

positive ALL, particularly when administered before allogeneic HSCT. Given that patients can experience relapse following allogeneic HSCT, strategies are needed to prevent disease recurrence. One such strategy involves the incorporation of post-HSCT maintenance therapy with TKIs, which has been investigated in several studies. In a small prospective study in patients with Ph-positive leukemias who underwent allogeneic HSCT (n = 15 with ALL; median age 37 years, range 4–49 years), imatinib was administered from the time of engraftment until 1 year after HSCT.<sup>140</sup> The median time after HSCT until initiation of imatinib was short, at 27 days (range, 21–39 days). Molecular remission (by PCR) was observed in 46% of patients (6 of 13) prior to HSCT and 80% (12 of 15) after HSCT. Two patients died after hematologic relapse and 1 patient died due to acute respiratory distress syndrome approximately 1 year post-HSCT. At a median follow up of 1.3 years, 12 patients (80%) remain alive without detectable disease.<sup>140</sup> This was one of the first prospective studies to show the feasibility of administering imatinib maintenance early in the post-HSCT period (<90 days) when the leukemic tumor burden tends to be low. Maintenance therapy with imatinib was also evaluated in a more recent prospective study in patients who underwent allogeneic HSCT (n = 82; median age 28.5 years; range, 3–51 years).<sup>141</sup> Imatinib was scheduled for a period of 3 to 12 months (until three consecutive tests were negative for *BCR-ABL* transcripts or sustained molecular CR for at least 3 months). Among the patients who received imatinib (n = 62), the median time after HSCT until initiation of imatinib was 70 days (range, 20–270 days). In this group of patients, 84% were alive with a molecular CR at a median follow up of 31 months.<sup>141</sup> Imatinib was discontinued in 16% of patients receiving treatment due to toxicities. The remaining patients (n = 20) who did not receive maintenance with imatinib (due to cytopenias, infections, GVHD or patient choice) constituted the non-imatinib group. The estimated 5-year relapse rate was significantly

lower with imatinib compared with no imatinib (10% vs. 33%;  $P = .0016$ ) and the estimated 5-year DFS (81.5% vs. 33.5%;  $P < .001$ ) and OS rates (87% vs. 34%;  $P < .001$ ) were significantly longer with imatinib compared with no imatinib.<sup>141</sup>

The previous study was not designed as a randomized controlled trial, and the number of patients in the non-imatinib group was small. A recent multicenter randomized trial evaluated imatinib given prophylactically ( $n = 26$ ) compared with imatinib given at the time of MRD detection (ie, molecular recurrence;  $n = 29$ ) in patients who underwent allogeneic HSCT with a planned duration of imatinib therapy for 1 year.<sup>142</sup> MRD was defined by appearance of *BCR-ABL* transcripts, as assessed by quantitative RT-PCR performed at a central laboratory. In the prophylactic arm, imatinib was started in 24 patients (92%) at a median time of 48 days (range, 23–88 days) after HSCT. In the MRD-triggered arm, imatinib was started in 14 patients (48%) at a median time of 70 days (range, 39–567 days) after HSCT. Imatinib was discontinued prematurely in the majority of patients in both arms (67% in the prophylaxis arm; 71% in the MRD-triggered arm), primarily because of toxicities.<sup>142</sup> Ongoing CR was observed in 81% of patients in the prophylaxis arm (median follow up 30 months) and 78% in the MRD-triggered arm (median follow up 32 months). No significant differences were found between the prophylaxis and MRD-triggered arms in terms of relapse rate (8% vs. 17%), 5-year DFS (84% vs. 60%), EFS (72% vs. 54%), or OS (80% vs. 74.5%).<sup>142</sup> However, MRD positivity was predictive of relapse regardless of treatment arm; the 5-year RFS rate was significantly lower among patients with detectable MRD compared with those who remained MRD negative (70% vs. 100%;  $P = .017$ ). Moreover, early MRD positivity (within 100 days after HSCT) was associated with significantly decreased EFS compared with late MRD detection (median 39 months vs. not reached; 4-year EFS

39% vs. 65%;  $P = .037$ ).<sup>142</sup> This trial suggested that imatinib given post-allogeneic HSCT (either prophylactically or based on MRD detection) resulted in low relapse rates and durable remissions. However, imatinib may not provide benefit for patients who experience early molecular relapse or persistent MRD following HSCT. Although no randomized controlled trials have yet been conducted to establish the efficacy of TKIs (compared with observation only or other interventions) following allogeneic HSCT, the collective results from these studies suggest that TKI maintenance may have a potential role in reducing the risk for relapse.

A proportion of patients with Ph-positive ALL may be resistant to initial therapy with imatinib-containing regimens or may experience relapse after imatinib therapy; resistance to imatinib is attributed, at least partly, to the presence of point mutations within the *ABL* kinase domain.<sup>143-146</sup> Moreover, CNS relapse has been reported in both patients with disease responsive to imatinib therapy (isolated CNS relapse with CR in marrow) and patients with disease resistant to imatinib therapy.<sup>147-150</sup> The concentration of imatinib in the cerebrospinal fluid (CSF) has been shown to be approximately 2 logs lower than that achieved in the blood, suggesting that this agent does not adequately penetrate the blood-brain barrier to ensure CNS coverage.<sup>148,150</sup> A study showed that among patients with ALL treated with imatinib and who did not receive routine prophylactic intrathecal therapy or cranial irradiation, 12% developed CNS leukemia.<sup>149</sup> Patients with imatinib-resistant disease and developed CNS disease rapidly died from progressive disease; conversely, patients with imatinib-sensitive disease who developed isolated CNS relapse could be successfully treated with intrathecal therapy with or without cranial irradiation.<sup>147,149</sup>

Dasatinib is a second-generation TKI that inhibits both the *BCR-ABL* kinase and *SRC* family kinase, the latter of which is thought to be

involved in an alternative signaling pathway in imatinib-resistant ALL; moreover, dasatinib displayed a 325-fold increase in potency in inhibiting in vitro growth of cells with wild-type *BCR-ABL* compared with imatinib,<sup>151</sup> and maintained activity against cells harboring imatinib-resistant *ABL* kinase domain mutations, with the exception of the T315I, V299L, and F317L mutations.<sup>151-153</sup> In phase II and III dose-comparison studies, dasatinib showed activity in patients with relapsed or refractory ALL who could not tolerate or were resistant to imatinib.<sup>111,153,154</sup>

Additionally, dasatinib showed activity against CNS leukemia in preclinical in vivo models and in a small group of patients with Ph-positive ALL with CNS involvement.<sup>155</sup> Thus, it seems that dasatinib may provide some benefit over imatinib in terms of increased potency in inhibiting signaling pathways, activity against various *ABL* kinase mutations, and greater penetration of the blood-brain barrier.

Recent studies have shown the promising activity of dasatinib when incorporated into frontline regimens for patients with ALL. In a phase II study from MDACC, dasatinib was combined with hyper-CVAD and subsequent maintenance therapy in patients with previously untreated Ph-positive ALL (n = 35; median age, 53 years; range, 21–79 years; 31% were older than 60 years); 4 of the patients received allogeneic HSCT at first CR.<sup>113</sup> The 2-year OS and EFS rates were 64% and 57%, respectively. In a study from GIMEMA (LAL-1205), patients with Ph-positive ALL (n = 53 evaluable; median age, 54 years; range, 24–76.5 years) received induction therapy with dasatinib and prednisone.<sup>123</sup> Postinduction therapy included no further therapy (n = 2), TKI only (n = 19), TKI combined with chemotherapy (n = 10) with or without autologous HSCT (n = 4), or allogeneic HSCT (n = 18). All patients experienced a CR after induction therapy. The median OS was 31 months and the median DFS (calculated from day +85) was 21.5 months. At 20 months, the OS and DFS rates were 69% and 51%,

respectively.<sup>123</sup> T315I mutation was detected in 12 of 17 patients with relapsed disease (71%).

The treatment of older patients with Ph-positive ALL may pose a challenge, because elderly patients or those with comorbidities may not tolerate aggressive regimens with multiagent chemotherapy combined with TKIs. Several studies have evaluated outcomes with imatinib induction, with or without concurrent corticosteroids, in the older adult population with Ph-positive ALL. In a study that randomly assigned older patients with Ph-positive ALL (n = 55; median age, 68 years; range, 54–79 years; 94.5% were aged 60 years or older) to induction therapy with imatinib versus chemotherapy alone, followed by imatinib-containing consolidation therapy, the estimated 2-year OS rate was 42%; no significant difference was observed between induction treatment arms.<sup>112</sup> The median OS was numerically higher (but not statistically significant) among patients who received imatinib induction compared with those randomized to chemotherapy induction (23.5 vs. 12 months). However, the incidence of severe adverse events was significantly lower with imatinib induction (39% vs. 90%; *P* = .005), which suggested that induction therapy with imatinib may be better tolerated than chemotherapy in older patients with Ph-positive ALL.<sup>112</sup> In a small phase II study from GRAALL (AFR-09 study), older patients (age ≥55 years) with Ph-positive ALL (n = 29 evaluable; median age, 63 years) were treated with chemotherapy induction followed by a consolidation regimen with imatinib and methylprednisolone.<sup>156</sup> The 1-year OS rate in this study was significantly higher compared with that for the historical control population who received the same induction therapy but did not receive imatinib as part of consolidation (66% vs. 43%; *P* = .005), and the median OS in this study was longer than that of control group (23 vs. 11 months, respectively). In addition, the 1-year RFS rate was significantly increased with the addition of imatinib (58%

vs. 11%;  $P < .001$ ).<sup>156</sup> A phase II study by GIMEMA (LAL0201-B study) also evaluated imatinib combined with corticosteroids in older patients (age >60 years) with Ph-positive ALL (n = 29 evaluable; median age, 69 years).<sup>157</sup> Patients received imatinib in combination with prednisone for induction. The estimated 1-year DFS and OS rates were 48% and 74%, respectively; the median OS was 20 months.<sup>157</sup>

In a recent European multicenter trial (EWALL-Ph-01 study), induction therapy with dasatinib combined with low-intensity chemotherapy (vincristine and dexamethasone) was evaluated in older patients (age ≥55 years) with Ph-positive ALL (n = 71; median age 69 years; range, 58–83 years).<sup>158</sup> The CR rate after induction was 94%; MRD response (*BCR-ABL* / *ABL* ratio ≤0.1%) occurred in 54% of patients and 22% had undetectable MRD. The estimated 3-year RFS and OS was 43% and 45%, respectively.<sup>158</sup> Relapse occurred in 29 patients (41%) after a median of 9 months (range, 3–34 months); 24 patients died. The *ABL* mutation T315I was found in 63% of relapsed cases; mutations in F317L and V299L were found in 7% and 4% of relapsed cases, respectively.<sup>158</sup> These studies suggest that the use of TKIs, either alone or in combination with less intensive therapies (eg, corticosteroids with or without vincristine), may provide an alternative treatment option for older patients with Ph-positive ALL for whom intensive regimens are not appropriate.

### 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 to 6 months, and a 5-year OS rate of 3% to 10% among patients who experience relapse after initial treatment.<sup>159-162</sup> One of the major factors 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 patients who experienced relapse in the PETHEMA trials, those who relapsed more than 2 years after frontline therapy had significantly higher 5-year OS rates than the groups of patients who did within 1 to 2 years or within 1 year of frontline therapy (31% vs. 15% vs. 2%;  $P < .001$ ).<sup>160</sup> Similarly, in the MRC UKALL XII/ECOG 2993 trial, patients with disease that relapsed more than 2 years after initial diagnosis and frontline therapy had a significantly higher 5-year OS rate than those who relapsed within 2 years (11% vs. 5%;  $P < .001$ ).<sup>159</sup> In the pre-imatinib era, patients with Ph-positive ALL who relapsed after frontline therapy had dismal outcomes; subgroup data from the large, prospective trials LALA-94 and MRC UK XII/ECOG 2993 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.<sup>159,161</sup>

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 primary refractory to or that relapses after initial treatment with TKI-containing regimens. Point mutations within the *ABL* kinase domain and alternative signaling pathways mediated by the SRC family kinase have been implicated in the mechanisms of resistance to imatinib.<sup>143-146,152,163</sup> Mutations within the *ABL* kinase domain have been identified in a large proportion of patients who experience disease recurrence after imatinib-containing therapy.<sup>144,145</sup> Moreover, *ABL* kinase domain mutations may be present in a small group of imatinib-naïve patients even before initiation of any TKI therapy.<sup>164,165</sup> 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.<sup>151-153,166,167</sup> Both TKIs have been evaluated as single-agent therapy in patients with Ph-positive ALL that are resistant or intolerant to imatinib treatment.<sup>109,111,154</sup> A randomized phase III study examined the activity of dasatinib administered as once-daily (140 mg daily) versus twice-daily (70 mg twice daily) dosing in patients with Ph-positive leukemia resistant to imatinib.<sup>154</sup> In the group of patients with Ph-positive ALL (n = 84), the once-daily dosing resulted in higher response rates (major cytogenetic response) than the twice-daily dosing (70% vs. 52%), and although the median OS was shorter with the once-daily dosing (6.5 vs. 9 months), the median progression-free survival was longer (4 vs. 3 months).<sup>154</sup> 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 who are intolerant or resistant to prior therapy.

Not all imatinib-resistant *ABL* mutations are susceptible to the newer TKIs, however. For instance, dasatinib is not as active against cells harboring the *ABL* mutations T315I, V299L, and F317L.<sup>146,151-153,168-170</sup> 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 chronic myelogenous leukemia, and treatment options according to the presence of different *ABL* mutations.<sup>171</sup>

Ponatinib is another TKI that was initially approved by the FDA in December 2012 for the treatment of adult patients with chronic, accelerated, or blast phase Ph-positive chronic myelogenous leukemia (CML) or Ph-positive ALL, with resistance or intolerance to prior therapy.<sup>172</sup> Though temporarily removed from the market in November

2013, ponatinib distribution resumed in December 2013 following revision to both the prescribing information and REMS program that addressed the risk for serious cardiovascular adverse events. This TKI has been shown to inhibit both native BCR-ABL and mutant forms of BCR-ABL (including those resulting from T315I mutation) in preclinical studies.<sup>107,172</sup> 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).<sup>107</sup> 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.<sup>107</sup> In the multicenter open-label phase II study (PACE trial; n = 449 enrolled; median age 59 years, range 18–94), ponatinib showed substantial activity in patients with Ph-positive leukemias resistant or intolerant to second-generation TKIs.<sup>110</sup> Patients on 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) 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 progression-free survival 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.<sup>110</sup> No significant differences in duration or OS outcomes were apparent based on *ABL* T315I mutation status; however, the patient numbers were small.<sup>110</sup> The most common treatment-related adverse events in the PACE trial overall

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.<sup>110</sup> 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 is a new TKI that acts as a dual inhibitor of BCR-ABL and SRC family kinases.<sup>173,174</sup> This agent was approved (in 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 either chronic, accelerated or blast phase CML previously treated with at least one prior TKI therapy; all patients had received prior imatinib therapy.<sup>174</sup> 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 HSCT. 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 HSCT.<sup>175,176</sup> The patients subsequently received a second allogeneic HSCT. The use of donor lymphocyte infusion (DLI) to induce further graft-versus-leukemia effect in patients experiencing disease relapse after allogeneic HSCT has been evaluated in several case reports and small studies. Studies have reported little to no benefit of using DLI in patients with Ph-positive ALL who experience disease relapse after HSCT, though it has been suggested that this is due to a leukemic burden that may have been too high to control effectively.<sup>177,178</sup> Indeed, published case reports have suggested that the use of DLI for residual disease or molecular relapse

(as noted by levels of *BCR-ABL* fusion mRNA measured with PCR) after allogeneic HSCT may eliminate residual leukemic clones and thereby prevent overt hematologic relapse.<sup>179-181</sup> Moreover, case reports have suggested using newer TKIs, such as dasatinib and nilotinib, along with DLI for managing relapse after allogeneic HSCT.<sup>182,183</sup> A case report described the treatment course and outcome in a patient who experienced early hematologic relapse after allogeneic HSCT (performed in first CR), responded to imatinib-based multiagent chemotherapy and DLI (with persistent residual disease based on BCR-ABL transcripts), but then experienced a second hematologic relapse.<sup>184</sup> 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 HSCT and maintained a molecular CR lasting 18 months.<sup>184</sup> 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.

One of the early treatments for patients with advanced ALL included adoptive cell therapy to induce a graft versus leukemia effect through allogeneic hematopoietic stem cell transplant or donor leukocyte infusion; 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 chimeric antigen receptor (CAR) T cells to treat ALL is a significant advancement in the field.<sup>185-187</sup> Briefly, T cells from the patient are harvested and engineered with a receptor that targets a cell surface tumor-specific antigen (ie CD19 antigen on the surface of leukemic cells). The ability of CAR T cells to be modified is a significant advantage as they can be reprogrammed to target any cell-surface

antigen on leukemic cells, avoiding the issue of receptor down regulation, a process by which tumors evade detection by the immune system.<sup>188</sup> The CAR T cells are also engineered to contain a viral vector that will cause T cell expansion and proliferation following antigen recognition.<sup>189</sup> Once modified, CAR T cells are expanded ex vivo for approximately two weeks after which they are IV infused back into the patient.<sup>189</sup> CAR T cells can be produced in high numbers making this a feasible option in the clinical setting. Following infusion, debulking of tumors occurs in less than a week and these cells may remain in the body for extended periods of time where they can provide immunosurveillance against relapse.

Clinical trials in ALL patients with relapsed/refractory disease have shown promising results. There are several trials using CAR T cells that differ in the receptor construct. One of these trials uses the modified receptor termed 19-28z. Altogether, 22 pediatric ALL patients and 16 adult patients with relapsed or refractory B-cell ALL were given 19-28z CAR T cells. Of these 38 patients, an overall complete response to treatment was achieved in 19 of the pediatric<sup>187</sup> and 14 of the adult<sup>190</sup> patients. Fourteen pediatric patients have ongoing remission (greater than 18 months) and 5 pediatric patients relapsed.<sup>187</sup> Despite the incidence of relapse, the average remission rate for patients treated with CAR T-cell therapy (88%)<sup>190</sup> is still significantly improved compared to the average remission rate for patients receiving standard-of-care chemotherapy following relapse (approximately 30%).<sup>159,191,192</sup> For adult patients, 7 out of 16 patients were able to receive an allogeneic stem cell transplant (SCT), suggesting that CAR T cells may provide a bridge to allo-SCT.<sup>190</sup> A second receptor construct that is defined by the alteration in the single chain variable fragment (scFv) of CD19 (anti-CD19 scFv/4-1BB/CD3ζ) has shown similar results to the 19-28z CAR T cells in terms of overall complete response.<sup>193</sup> These cells, more

simply referred to as CTL019, were infused into 16 children and 4 adults with relapsed/refractory ALL.<sup>193</sup> Of these 20 patients, a complete response of the disease following therapy was achieved in 14 patients. There was no response of the disease to treatment in 3 patients and disease response to therapy for an additional 3 patients is still under evaluation. 3 did not respond and 3 are currently still under evaluation.<sup>193</sup>

Currently, bone marrow transplant is the only cure for ALL but many patients are not eligible for transplant based on age or progression of the disease. The pre-treatment of patients with CAR T cells has served as a bridge for transplant, and patients who were formally unable to be transplanted due to poor remission status, are now seeing complete remission and ultimately transplantation. There are fewer side effects to this treatment compared to the current standard-of-care regimens and all 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.<sup>190</sup> Based on their ability to elicit a significant response towards elimination of tumor cells, multi-center Phase II studies are planned for CAR T cells in the treatment of relapsed/refractory ALL.

### **NCCN Recommendations for Ph-Positive ALL**

#### ***AYA Patients (Age 15–39 Years) With Ph-Positive ALL***

The panel recommends that AYA patients with Ph-positive ALL be treated on a clinical trial, when possible. In the absence of an appropriate clinical trial, the recommended induction therapy would comprise multiagent chemotherapy combined with a TKI. Treatment

regimens should include adequate CNS prophylaxis for all patients. It is also important to adhere to the treatment regimens for a given protocol in its entirety, from induction therapy to consolidation/delayed intensification to maintenance therapy. For AYA patients experiencing a CR after initial induction therapy, consolidation with allogeneic HSCT should be considered if a matched donor is available. However, in younger AYA patients (age  $\leq 21$  years), emerging data suggest that allogeneic HSCT may not confer an advantage over chemotherapy combined with TKIs.<sup>114</sup> After HSCT, maintenance therapy (for 2–3 years) with a TKI, with or without monthly pulses of vincristine/prednisone, is recommended. Weekly methotrexate and daily 6-MP may be added to the maintenance regimen, as tolerated; however, the doses of these antimetabolite agents may need to be reduced in the setting of hepatotoxicity or myelosuppression. For patients without a donor, consolidation therapy after a CR should comprise a continuation of multiagent chemotherapy combined with a TKI. These patients should continue to receive postconsolidation maintenance therapy with a regimen that includes a TKI. Individuals who inherit a nonfunctional variant allele of the TPMT gene are known to be at high risk for developing hematopoietic toxicity (in particular, severe neutropenia) after treatment with 6-MP.<sup>103</sup> Testing for TPMT gene polymorphism should be considered in patients receiving 6-MP as part of maintenance therapy, particularly those who experience severe bone marrow toxicities.

The treatment approach for AYA patients experiencing less than a CR after initial induction therapy (ie, having primary refractory disease) would be similar to that for patients with relapsed/refractory ALL (see *Patients With Relapsed/Refractory Ph-Positive ALL*).

#### **Adult Patients (Age $\geq 40$ Years) With Ph-Positive ALL**

For adult patients with Ph-positive ALL, the panel recommends treatment on a clinical trial, when possible. In the absence of an appropriate clinical trial, the recommended induction therapy would initially depend on the patient's age and/or presence of comorbid conditions. Treatment regimens should include adequate CNS prophylaxis for all patients, and a given treatment protocol should be followed in its entirety. Although the age cutoff indicated in the guidelines has been set at 65 years, it should be noted that chronologic age alone is not a sufficient surrogate for defining fitness; patients should be evaluated on an individual basis to determine fitness for therapy based on factors such as performance status, end organ function, and end organ reserve.

For relatively fit adult patients (age  $< 65$  years or with no substantial comorbidities), the recommended treatment approach is similar to that of AYA patients. Induction therapy would comprise multiagent chemotherapy combined with a TKI. For patients experiencing a CR after induction, consolidation with allogeneic HSCT should be considered if a matched donor is available. After HSCT, maintenance therapy (for 2–3 years) with a TKI, with or without monthly pulses of vincristine/prednisone for 2–3 years is recommended. Weekly methotrexate and daily 6-MP may be added to the maintenance regimen, as tolerated; however, the doses of these antimetabolite agents may need to be reduced in the setting of hepatotoxicity or myelosuppression. For patients without a donor, consolidation therapy after a CR should comprise a continuation of multiagent chemotherapy combined with a TKI. These patients should continue to receive postconsolidation maintenance therapy with a regimen that includes a TKI. Again, testing for TPMT gene polymorphism should be considered for patients receiving 6-MP as part of maintenance therapy, especially those who develop severe bone marrow toxicities after its initiation. For

patients with less than a CR after induction, the treatment approach would be similar to that for patients with relapsed/refractory disease (see later discussion).

For adult patients who are less fit (age  $\geq 65$  years or with substantial comorbidities), the recommended induction therapy includes a TKI with corticosteroids or with chemotherapy regimens. Dose modifications may be required for chemotherapy agents, as needed. Patients with a CR to induction should continue consolidation therapy with a TKI with or without corticosteroids or a TKI with or without chemotherapy; maintenance therapy (for 2–3 years) with a TKI, with or without monthly pulses of vincristine/prednisone for 2–3 years is recommended. Weekly methotrexate and daily 6-MP may be added to the maintenance regimen, as tolerated; however, the doses of antimetabolites may need to be reduced in the setting of hepatotoxicity or myelosuppression. Adult patients with less than a CR after induction should be managed similar to those with relapsed/refractory disease (see discussion section below).

#### ***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. The panel has largely adopted the recommendations for treatment options based on *ABL* mutation status for CML, as published by the European LeukemiaNet.<sup>171</sup> 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 the T315I mutation and is effective in treating. 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 on 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 HSCT if a donor is available. For patients with disease that relapses after an initial allogeneic HSCT, other options may include a second allogeneic HSCT and/or DLI.

## **Management of Ph-Negative ALL**

### **Initial Treatment in AYAs With Ph-Negative ALL**

The AYA population with ALL can pose a unique challenge given that these patients may be treated with either a pediatric or an adult protocol, depending on local referral patterns and institutional practices. Retrospective analyses based on cooperative group studies from both the United States and Europe have consistently shown the superior outcomes for AYA patients (age 15–21 years) treated on pediatric versus adult ALL regimens. In the AYA population, 5-year EFS rates ranged from 63% to 74% for patients treated on a pediatric study protocol versus 34% to 49% for those receiving the adult protocol.<sup>60,61,77,194,195</sup> In a recent retrospective comparative study that analyzed outcomes of AYA patients (age 16–20 years) treated on a

pediatric CCG study protocol (n = 197; median age, 16 years) versus an adult CALGB study protocol (n = 124; median age, 19 years), the 7-year EFS rate was significantly improved for those treated on the pediatric regimen compared with those on the adult regimen (63% vs. 34%;  $P < .001$ ); the 7-year OS rate was 67% versus 46%, respectively ( $P < .001$ ).<sup>77</sup> Moreover, AYA patients treated on the adult protocol experienced a significantly higher rate of isolated CNS relapse at 7 years (11% vs. 1%;  $P = .006$ ). The substantial improvements in outcomes observed with the pediatric regimen in this study, and in the earlier retrospective analyses from other cooperative groups, may be attributed largely to its use of greater cumulative doses of drugs, such as corticosteroids (prednisone and/or dexamethasone), vincristine, and L-asparaginase, and to earlier, more frequent, and/or more intensive CNS-directed therapy compared with adult regimens.<sup>77</sup>

Favorable outcomes with the use of pediatric-based treatment protocols in the AYA population have also been reported in other recent studies. In an analysis of outcomes in children and AYA patients treated in the Dana-Farber Cancer Institute (DFCI) ALL Consortium Protocols (1991–2000), the 5-year EFS rate among younger AYA patients (age 15–18 years; n = 51) was 78%, which was not significantly different from the EFS rates observed for children aged 10 to 15 years (77%; n = 108) or those aged 1 to 10 years (85%; n = 685).<sup>196</sup> The CCG 1961 study was designed to evaluate the benefit of augmented versus standard postinduction intensification therapy in children aged 1 to 9 years with high WBC counts ( $\geq 50 \times 10^9/L$ ) or in older children and adolescents aged 10 to 21 years.<sup>76</sup> Patients were stratified by their initial response to induction therapy as either slow early responders (patients with  $>25\%$  bone marrow blasts on day 7 of induction) or rapid early responders. Among the patients who were rapid early responders to induction (n = 1299), the augmented postinduction intensity arm was

associated with significantly increased rates of 5-year EFS (81% vs. 72%;  $P < .0001$ ) and OS (89% vs. 83%;  $P = .003$ ) compared with the standard-intensity arm.<sup>76</sup> In the subgroup of AYA patients (age 16–21 years; n = 262) from the CCG 1961 study treated with either augmented or standard-intensity regimens, the 5-year EFS and OS rates were 71.5% and 77.5%, respectively.<sup>197</sup> Among the AYA patients who were considered rapid early responders, the augmented-intensity (n = 88) and standard-intensity (n = 76) arms showed no statistically significant differences in rates of 5-year EFS (82% vs. 67%, respectively) or OS (83% vs. 76%, respectively). For the AYA patients who were considered slow early responders (all of whom received the augmented-intensity regimen), the 5-year EFS rate was 71%.<sup>197</sup>

Data from the most recent Total Therapy (XV) study by the St. Jude Children's Research Hospital also showed dramatic improvements in survival outcomes for the AYA population. In this study, patients were primarily risk-stratified based on treatment response; patients were treated according to risk-adjusted intensive chemotherapy, with the incorporation of minimal residual disease (MRD) evaluation during induction (day 19) to determine the need for additional doses of asparaginase.<sup>198,199</sup> The 5-year EFS rate for the AYA population (age 15–18 years; n = 45) was 86% (95% CI, 72%–94%), which was not significantly different from the 87% EFS rate (95% CI, 84%–90%;  $P = .61$ ) observed for the younger patients (n = 448). The 5-year OS rates for the AYA patients and younger patients were 88% and 94%, respectively ( $P =$  not significant).<sup>198,199</sup> The favorable EFS and OS outcomes in AYA patients in this study were attributed partly to the use of intensive dexamethasone, vincristine, and asparaginase, in addition to early intrathecal therapy (ie, triple intrathecal chemotherapy with cytarabine, hydrocortisone, and methotrexate) for CNS-directed therapy. In addition, the use of prophylactic cranial irradiation was

safely omitted in this study; the 5-year cumulative incidence of isolated CNS relapse and any CNS relapse was 3% and 4%, respectively, for the entire study population (n = 498).<sup>198</sup> Moreover, all 11 patients with isolated CNS relapse were children younger than 12 years. This study showed that, with intensive risk-adjusted therapy and effective CNS-directed intrathecal regimens, AYA patients can obtain long-term EFS without the need for cranial irradiation or routine allogeneic HSCT.<sup>198,199</sup>

Given the success seen with multiagent intensive chemotherapy regimens for pediatric patients with ALL, several clinical trials have evaluated pediatric-inspired regimens for the AYA patient population. In one of these trials (PETHEMA ALL-96), adolescent (n = 35; age 15–18 years) and young adult (n = 46; age 19–30 years) patients with standard-risk Ph-negative ALL [defined as WBC count  $<30 \times 10^9/L$ ; absence of t(9;22), t(1;19), t(4;11), or any other 11q23 rearrangements] received frontline therapy with a 5-drug induction regimen (vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide), consolidation/reinduction, and maintenance, along with triple intrathecal therapy throughout the treatment period.<sup>200</sup> The 6-year EFS and OS rates for the entire patient cohort was 61% and 69%, respectively. No difference in EFS rate was observed between adolescents (60%; 95% CI, 43%–77%) and adults (63%; 95% CI, 48%–78%); similarly, no significant difference was observed in OS rate for adolescents (77%; 95% CI, 63%–91%) versus adults (63%; 95% CI, 46%–80%).<sup>200</sup> Based on multivariate regression analysis, slow response to induction therapy (defined as having  $>10\%$  blast cells in the bone marrow aspirate performed on day 14 of treatment) was the only factor associated with a poor EFS (odds ratio [OR], 2.99; 95% CI, 1.25–7.17) and OS (OR, 3.26; 95% CI, 1.22–8.70).<sup>200</sup>

A multicenter phase II trial evaluated a pediatric-inspired regimen (based on the DFCI Childhood ALL Consortium Protocol 00-01) in AYA

and adult patients (age 16–50 years) with previously untreated ALL; 20% of the patients in this study had Ph-positive disease.<sup>201</sup> The treatment regimen comprised induction (vincristine, doxorubicin, prednisone, L-asparaginase, and high-dose methotrexate), triple intrathecal therapy, intensification, and maintenance. Among the 75 patients with evaluable data, the estimated 2-year EFS and OS rates were 72.5% and 77%, respectively.<sup>201</sup> Adverse events included 1 death from sepsis (during induction), pancreatitis in 9 patients (12%; including 1 death), osteonecrosis in 2 patients (3%), thrombosis/embolism in 14 patients (19%), and neutropenic infection in 23 patients (31%).<sup>201</sup> Although this intensive regimen was feasible in adult patients, further follow-up data are needed to evaluate long-term survival outcomes.

The prospective phase II GRAALL-2003 study evaluated a pediatric-inspired regimen (using intensified doses of vincristine, prednisone, and asparaginase) for adolescents and adults with Ph-negative ALL (n = 225; median age, 31 years; range, 15–60 years).<sup>202</sup> The induction regimen comprised vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide. Patients with high-risk disease and donor availability were allowed to proceed to allogeneic HSCT. The EFS and OS rates at 42 months were 55% and 60%, respectively. When data from patients who underwent transplantation at first CR were censored, the DFS rates at 42 months were 52% for patients with high-risk disease and 68% for patients with standard-risk disease (risk assignment based on GRAALL protocol); these DFS outcomes by risk groups were similar to outcomes using the MRC UKALL/ECOG definition for risk classification.<sup>202</sup> Advanced age was predictive of poorer survival outcomes on this study; the OS rate at 42 months was 41% for patients older than 45 years compared with 66% for those aged 45 years or younger. Moreover, advanced age (using 45 years as the cutoff) was associated with a higher cumulative incidence of

therapy-related deaths (23% vs. 5%) and deaths in first CR (22% vs. 5%).<sup>202</sup> Thus, it seems that the benefit of this pediatric-inspired regimen outweighed the risks for therapy-related deaths only for those patients up to 45 years of age with Ph-negative ALL.

A multicenter phase II Intergroup study (CALGB 10403) is currently ongoing to evaluate a pediatric-inspired regimen in the treatment of AYA patients with Ph-negative ALL (eligible patients are age 16–39 years). One of the objectives of this study is to compare the outcomes of patients treated on this trial with those of a similar group of patients (in regard to age and disease characteristics) treated by pediatric oncologists on the COG trial (AALL-0232). The treatment protocol includes a 4-drug induction regimen with intrathecal cytarabine and intrathecal methotrexate, consolidation, interim maintenance, delayed intensification, maintenance (for 2–3 years), and radiotherapy (for patients with testicular or CNS disease or those with T-cell ALL).

For patients with T-cell ALL, the addition of nelarabine may be a promising approach. Nelarabine is a nucleoside metabolic inhibitor and a prodrug of nelarabine, approved for the treatment of patients with T-cell ALL with disease that has not responded to or that has relapsed after at least 2 chemotherapy regimens.<sup>203</sup> This drug is currently under evaluation as part of frontline chemotherapy regimens in AYA patients with T-cell ALL. The initial safety results from the randomized phase III COG study (AALL-0434) of the augmented BFM chemotherapy regimen, with or without nelarabine, showed that the toxicity profiles were similar between patients with high-risk T-cell ALL who received nelarabine (n = 28) and those who did not (n = 29).<sup>204</sup> No significant differences were observed in the occurrence of neurologic adverse events between these groups, including peripheral motor neuropathy, peripheral neuropathy, or CNS neurotoxicity. The incidence of adverse events such as febrile neutropenia and elevation of liver enzymes was

also similar between treatment groups. These initial safety data suggest that nelarabine may be better tolerated in frontline regimens than in the relapsed/refractory setting.<sup>204</sup> Results from the efficacy phase of this study are awaited.

For AYA patients in first CR, allogeneic HSCT may be considered for high-risk cases, such as those with elevated WBC counts and poor-risk cytogenetics (eg, hypodiploidy, *MLL* rearrangement) at diagnosis. A large multicenter trial (LALA-94 study) evaluated the role of postinduction HSCT as one of the study objectives in adolescent and adult ALL patients receiving therapy for previously untreated ALL (n = 922; median age, 33 years; range, 15–55 years).<sup>63</sup> Patients were stratified into 4 risk groups: 1) Ph-negative standard-risk disease [defined as achievement of CR after 1 course of chemotherapy; absence of CNS disease; absence of t(4;11), t(1;19), or other 11q23 rearrangements; WBC count <30 × 10<sup>9</sup>/L]; 2) Ph-negative high-risk ALL (defined as patients with non–standard-risk disease and without CNS involvement); 3) Ph-positive ALL; and 4) evidence of CNS disease. After induction therapy, patients with Ph-negative high-risk ALL were eligible to undergo allogeneic HSCT if a matched sibling donor was available; those without a sibling donor were randomized to undergo autologous HSCT or chemotherapy alone.<sup>63</sup> Among the subgroup of patients with Ph-negative high-risk ALL (n = 211), the 5-year DFS and OS rates were 30% (median, 16 months) and 38% (median, 29 months), respectively. Based on intent-to-treat analysis, outcomes in patients with Ph-negative high-risk ALL were similar for autologous HSCT (n = 70) and chemotherapy alone (n = 59) in terms of median DFS (15 vs. 11 months), median OS (28 vs. 26 months), and 5-year OS rate (32% vs. 21%).<sup>63</sup> Outcomes were improved in patients with Ph-negative high-risk ALL and those with CNS involvement allocated to allogeneic HSCT. The median DFS was 21 months for these patients,

and the median OS has not yet been reached; the 5-year OS rate was 51%.<sup>63</sup> Thus, it appeared that in patients with Ph-negative high-risk disease, allogeneic HSCT in first CR improved DFS outcomes, whereas autologous HSCT did not result in significant benefit compared with chemotherapy alone.

In the PETHEMA ALL-93 trial, adult patients with high-risk ALL [defined as 30–50 years of age; WBC count  $\geq 25 \times 10^9/L$ ; or t(9;22), t(4;11), or other 11q rearrangements, or t(1;19)] received postremission induction therapy (n = 222 eligible; median age, 27 years; range, 15–50 years) with allogeneic HSCT (n = 84; if matched related donor available), autologous HSCT (n = 50), or chemotherapy alone (n = 48).<sup>205</sup> Based on intent-to-treat analysis of data from patients with Ph-negative high-risk disease, no significant advantage was observed in a donor versus no-donor comparison of median DFS (21 vs. 38 months), median OS (32 vs. 67 months), 5-year DFS rate (37% vs. 46%), or 5-year OS rate (40% vs. 49%). In addition, when the analysis was conducted based on the actual postremission treatment received, no significant differences were noted between treatment arms for 5-year DFS rates (50% for allogeneic HSCT; 55% for autologous HSCT; 54% for chemotherapy alone).<sup>205</sup>

The role of allogeneic HSCT in adults with ALL was also evaluated in the large multicenter MRC UKALL XII/ECOG 2993 study (n = 1913; age 15–59 years).<sup>64</sup> In this study, high risk was defined as 35 years of age or older; time to CR greater than 4 weeks from induction; elevated WBC counts ( $>30 \times 10^9/L$  for B-cell ALL;  $>100 \times 10^9/L$  for T-cell ALL); or the presence of Ph chromosome; all others were considered to be standard risk. Patients experiencing a remission with induction therapy were eligible to undergo allogeneic HSCT if a matched sibling donor was available or, in the absence of a sibling donor, were randomized to undergo autologous HSCT or chemotherapy. The 5-year OS rate was

higher for patients randomized to chemotherapy alone compared with autologous HSCT (46% vs. 37%;  $P = .03$ ). A donor versus no-donor comparison in all patients with Ph-negative ALL showed that the 5-year OS rate was significantly higher in the donor group than the no-donor group (53% vs. 45%;  $P = .01$ ). This advantage in OS outcomes for the donor group was observed for patients with standard risk (62% vs. 52%;  $P = .02$ ) but not for those with Ph-negative high-risk disease (41% vs. 35%).<sup>64</sup> This was partly because of the high rate of nonrelapse mortality observed with the donor group compared with the no-donor group in patients with high-risk disease (36% vs. 14% at 2 years). Among patients with standard risk, the nonrelapse mortality rate at 2 years was 19.5% for the donor group and 7% for the no-donor group. Relapse rate was significantly lower in the donor group than the no-donor group for both patients with standard risk (24% vs. 49%;  $P < .001$ ) and those with high risk (37% vs. 63%;  $P < .001$ ).<sup>64</sup> Nevertheless, the high nonrelapse mortality rate in the donor group among patients with high-risk disease seemed to diminish the advantage of reduced risks for relapse in this group. This study suggested that allogeneic HSCT in first CR was beneficial in patients with standard-risk ALL.

The benefit of matched sibling allogeneic HSCT in adult patients with standard-risk ALL was also reported by the HOVON cooperative group. In a donor versus no-donor analysis of patients with standard-risk ALL undergoing postremission therapy with matched sibling allogeneic HSCT or autologous HSCT, the donor arm was associated with a significantly reduced 5-year relapse rate (24% vs. 55%;  $P < .001$ ) and higher 5-year DFS rate (60% vs. 42%;  $P = .01$ ) compared with the no-donor arm.<sup>206</sup> In the donor group, the nonrelapse mortality rate at 5 years was 16% and the 5-year OS rate was 69%.<sup>206</sup>

As evidenced by the previously described studies, matched sibling HSCT has been established as a valuable treatment strategy for

patients with high-risk Ph-negative ALL, but more recently unrelated donor (URD) transplants have been proposed. In a retrospective analysis of 169 patients who underwent URD HSCT during first CR, 60 patients (36%) had one poor prognostic factor and 97 (57% had multiple risk factors). The 5-year survival was 39% which is higher than survival reported in studies of high-risk patients receiving chemotherapy alone.<sup>207</sup> The most significant percentage of treatment-related mortality occurred in patients that were given mismatched donors compared to partially or well-matched donors. This study further demonstrated no significant difference in outcome between older and younger patients, suggesting that URD transplants may be an option for older patients. In a follow-up retrospective study by the same group, reduced-intensity conditioning (RIC) was incorporated to try to lower treatment-related mortality.<sup>208</sup> RIC conditioning most commonly comprised busulfan (9 mg/kg or less), melphalan (150 mg/m<sup>2</sup>), low dose total body irradiation (less than 500 cGy single dose or less than 800 cGy fractionated), or fludarabine plus total body irradiation of 200 cGy. RIC is more prominent in the treatment of older patients; therefore, the median age for patients receiving full intensity (FI) conditioning was 28 years (range, 16-62 years) and for patients receiving RIC, the median age was 45 years (range, 17-66 years). Despite the variation in age, results from the study have shown no difference in relapse at 3 years (35% vs. 26%,  $P = .08$ ) or in treatment-related mortality at 3 years (FI 33%; 95% CI, 31%-36% vs. RIC 32%; 95% CI, 23%-43%,  $P = .86$ ).<sup>208</sup> The 3-year survival for HSCT was similar following CR1 (FI 51%; 95% CI, 48%-55% vs. RIC 45%; 95% CI, 31-59%) and CR2 (FI 33%; 95% CI, 30%-37% vs. RIC 28%; 95% CI, 14%-44%). The DFS was also similar in both groups following CR1 (FI 49%; 95% CI, 45%-53% vs. RIC 36%; 95% CI, 23%-51%) and in CR2 (FI 32%; 95% CI, 29%-36% vs. RIC 27%; 95% CI, 14%-43%).<sup>208</sup>

A systemic review and meta-analysis of published randomized trials on postremission induction therapy in adults with ALL reported a significant reduction in all-cause mortality with allogeneic HSCT in first CR (RR, 0.88; 95% CI, 0.80–0.97) compared with autologous HSCT or chemotherapy.<sup>209</sup> A subgroup analysis showed a significant survival advantage with allogeneic HSCT in standard-risk ALL, whereas a nonsignificant advantage was seen in high-risk ALL.<sup>209</sup> Autologous HSCT in first remission was not shown to be beneficial relative to chemotherapy, as shown by several large studies and meta-analyses.<sup>63,64,209,210</sup>

### Initial Treatment in Adults With Ph-Negative ALL

Typically, induction regimens for adult ALL are also based on a backbone of vincristine, corticosteroids, and anthracyclines. The CALGB 8811 trial evaluated a 5-drug induction regimen (comprising vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide) as part of an intensive chemotherapy regimen for patients with previously untreated ALL (n = 197; Ph-positive in 29%; median age, 32 years; range, 16–80 years).<sup>78</sup> The median OS for all patients was 36 months, after a median follow-up of 43 months. Among patients who experienced a CR (85% of all patients), the median remission duration was 29 months. The estimated 3-year OS rate was higher for the subgroup of patients younger than 30 years compared with those aged 30 to 59 years (69% vs. 39%). Among the subgroup of patients who had both Ph-negative and BCR-ABL–negative disease (n = 57), median OS was 39 months and the 3-year OS rate was 62%.<sup>78</sup> Linker et al<sup>211</sup> evaluated an intensified chemotherapy regimen that incorporated a 4-drug induction regimen (comprising vincristine, daunorubicin, prednisone, and asparaginase) in adolescent and adult patients with ALL (n = 84; Ph-positive in 16%; median age, 27 years; range, 16–59 years). The 5-year EFS and OS rates for all patients were

48% and 47%, respectively. Among the patients who experienced a CR (93% of all patients), the 5-year EFS rate was 52%. Among the subgroup of patients without high-risk features ( $n = 53$ ), the 5-year EFS rate was 60%.<sup>211</sup>

In one of the largest multicenter prospective trials conducted to date (MRC UKALL XII/ECOG 2993 study), previously untreated adolescent and adult patients ( $n = 1521$ ; age 15–59 years) received induction therapy comprising vincristine, daunorubicin, prednisone, and L-asparaginase for 4 weeks (phase I) followed by cyclophosphamide, cytarabine, oral 6-MP, and intrathecal methotrexate for 4 weeks (phase II).<sup>69</sup> After completion of induction therapy, patients who experienced a CR received intensification therapy with 3 cycles of high-dose methotrexate (with standard leucovorin rescue) and L-asparaginase. After intensification, those younger than 50 years who had an HLA-compatible sibling underwent allogeneic HSCT; all others were randomized to receive autologous HSCT or consolidation/maintenance treatment.<sup>69</sup> For Ph-negative disease, high risk was defined as having any of the following factors: age of 35 years or older; time to CR greater than 4 weeks; or elevated WBC count ( $>30 \times 10^9/L$  for B-cell lineage;  $>100 \times 10^9/L$  for T-cell lineage). All other Ph-negative patients were considered to have standard-risk disease. The 5-year OS rate for all patients with Ph-negative ALL was 41%; the OS rate for the subgroups with standard risk ( $n = 533$ ) and high risk ( $n = 590$ ) was 54% and 29%, respectively.<sup>69</sup> In the subgroup of patients with T-cell ALL ( $n = 356$ ), the 5-year OS rate was 48%; the OS rate was improved to 61% for those with a matched sibling donor, primarily because of lower incidence of cumulative relapse.<sup>212</sup> Among the patients with T-cell ALL, those with complex cytogenetic abnormalities had poor 5-year OS outcomes (19%).

The hyper-CVAD regimen constitutes another commonly used ALL treatment regimen for adult patients. A phase II study from MDACC evaluated hyper-CVAD in adolescents and adults with previously untreated ALL ( $n = 288$ ; median age, 40 years; range, 15–92 years; Ph-positive in 17%).<sup>83</sup> The median OS for all patients was 32 months and the 5-year OS rate was 38%, with a median follow-up of 63 months. Among patients who experienced a CR (92% of all patients), the 5-year CR duration rate was 38%.<sup>83</sup> Death during induction therapy occurred in 5% of patients, and was more frequent among patients aged 60 years or older. Among the patients with Ph-negative ALL ( $n = 234$ ), the 5-year OS rate was 42%.<sup>83</sup>

Based on retrospective analyses of data from adults with B-cell ALL treated in clinical trials, CD20 positivity (generally defined as CD20 expression on  $>20\%$  of blasts) was found to be associated with adverse outcomes in terms of a higher cumulative incidence of relapse, decreased CR duration, or decreased survival.<sup>29,213</sup> Given the prognostic significance of CD20 expression in these patients, treatment regimens incorporating the CD20 monoclonal antibody rituximab have been evaluated. A phase II study from MDACC evaluated hyper-CVAD with or without rituximab in previously untreated patients with Ph-negative B-lineage ALL ( $n = 282$ ; median age, 41 years; range, 13–83 years).<sup>119</sup> Among the subgroup of patients with CD20-positive ALL who were treated with hyper-CVAD combined with rituximab, the 3-year CR duration rate and OS rate was 67% and 61%, respectively. In addition, among the younger patients (age  $<60$  years) with CD20-positive disease, modified hyper-CVAD plus rituximab resulted in significantly improved CR duration (70% vs. 38%;  $P < .001$ ) and OS rates (75% vs. 47%;  $P = .003$ ) compared with the standard hyper-CVAD regimen without rituximab.<sup>119</sup> No significant differences in outcomes with the addition of rituximab were noted for the subgroup of patients with

CD20-negative disease. Notably, older patients (age  $\geq 60$  years) with CD20-positive disease did not seem to benefit from the addition of rituximab, partly because of a high incidence of death in CR among older patients.

For discussion of HSCT in first CR in adult patients with Ph-negative ALL, refer to *Initial Treatment in AYA With Ph-Negative ALL*.

### Treatment of Relapsed Ph-Negative ALL

Despite major advances in the treatment of childhood ALL, approximately 20% of pediatric patients experience relapse after initial CR to frontline treatment regimens.<sup>214-216</sup> Among those who experience relapse, only approximately 30% experience long-term remission with subsequent therapies.<sup>120,217,218</sup> 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%.<sup>214</sup> 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 time of diagnosis; late cases were defined as relapses occurring 36 months or more from diagnosis. For cases of isolated CNS relapse, the 5-year survival estimates among early ( $n = 175$ ), intermediate ( $n = 180$ ), and late ( $n = 54$ ) relapsing disease were 43.5%, 68%, and 78%, respectively ( $P < .0001$ ).<sup>214</sup> 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.<sup>214</sup> In a separate analysis of data from one of the above

COG studies (CCG-1952), the timing and site of first relapse was 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 WBC count  $< 50 \times 10^9/L$ ).<sup>219</sup> 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.<sup>219</sup> Similarly, early isolated extramedullary relapse (duration of first CR  $< 18$  months) was associated with significantly shorter estimated 3-year EFS (37% vs 71%;  $P = 0.01$ ) and OS (55% vs 81.5%;  $P = 0.039$ ) compared with late extramedullary relapse. In a multivariate regression analysis, early bone marrow and extramedullary relapse were independent predictors of poorer EFS outcomes.<sup>219</sup>

AYA and adult patients with ALL who 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 2993 study and PETHEMA studies, the median OS after relapse was only 4.5 to 6 months; the 5-year OS rate was 7% to 10%.<sup>159,160</sup> Approximately 20% to 30% of patients experience a second CR with second-line therapies.<sup>160,162</sup> Factors predictive of more favorable outcomes after subsequent therapies included younger age and a first CR duration of more than 2 years.<sup>135,160</sup> Among younger patients (age  $< 30$  years) whose disease relapsed after experiencing a first CR duration longer than 2 years with frontline treatment on PETHEMA trials, the 5-year OS rate from the time of first relapse was 38%.<sup>160</sup>

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 (age 1–21 years) with ALL that is relapsed or refractory after at least 2 prior regimens.<sup>220</sup> 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 + CR without platelet recovery [CRp]) was 20%.<sup>221</sup> 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 has 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.<sup>221</sup> 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.<sup>221,222</sup>

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.<sup>223</sup> 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%.<sup>224,225</sup> 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%.<sup>226</sup> 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 veno-occlusive disease (the latter occurring in the post-allogeneic HSCT setting).<sup>224-226</sup> 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.<sup>227</sup> The most common grade 3 or 4 toxicities included infection (58%) and liver toxicities (24%).<sup>227</sup> 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.<sup>228</sup> The combination of high-dose cytarabine and idarubicin was evaluated as a regimen in adult patients with relapsed/refractory ALL (n = 29).<sup>229</sup> 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 HSCT. The median OS for all patients on the study was 6 months.<sup>229</sup>

A phase II study from MDACC 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).<sup>230</sup> Among evaluable patients (n = 88), the CR rate was 47%; an additional 13% experienced a CRp and 5% a partial remission. The 30-day mortality rate was 9%, and was lower among the subgroup who received polyethylene glycol (PEG)-

asparaginase 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 HSCT.<sup>230</sup>

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 have relapsed disease after at least 2 chemotherapy regimens.<sup>203</sup> 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).<sup>120</sup> 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).<sup>122</sup> 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.<sup>122</sup>

Vincristine remains an important part of the back bone of chemotherapy agents used in ALL treatment. Vinca alkaloids are known to be associated with neurological 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.<sup>231</sup> 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).<sup>192</sup> Approximately 50% of patients had received 3 or more prior lines of therapy. In addition, 48% of patients had undergone prior HSCT, 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.<sup>192</sup> The incidence of early induction death (30-day mortality rate) was 12%.<sup>192</sup> 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%).<sup>192,232</sup> 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% (no grade 4).<sup>192</sup> 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.<sup>233</sup>

Novel monoclonal antibodies are currently under clinical investigation. Inotuzumab ozogamicin is an anti-CD22 antibody-drug conjugate that has shown high CR rates (57%) in a phase II study in patients with relapsed/refractory ALL (n = 49).<sup>234</sup> 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).<sup>235</sup> 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).<sup>236</sup> After a median follow up of 33 months, the hematologic RFS rate was 61%. These antibodies are investigational and are 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 HSCT over chemotherapy alone for adult patients with ALL experiencing a second CR.<sup>237</sup> Several studies have shown that for AYA patients in second CR, allogeneic HSCT may improve outcomes, particularly for patients who have early bone marrow relapse or have other high-risk factors, such as T-cell ALL.<sup>217,218,238</sup> In a retrospective analysis of 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 HSCT (n = 186) and those who received chemotherapy regimens on the POG trials (n = 188).<sup>238</sup> The study showed that among patients with early bone marrow relapse (<36 months from time of diagnosis), total body irradiation (TBI)-containing allogeneic HSCT 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 HSCT was not observed among the subgroup with a late first relapse (≥36 months), and no advantages were seen with the use of non-TBI-containing HSCT regimens regardless of the timing of first relapse.<sup>238</sup> Thus, among patients with pre-B-cell ALL in

second CR after early bone marrow relapse, TBI-containing allogeneic HSCT may improve outcomes compared with chemotherapy alone; however, for patients with late bone marrow relapse, HSCT may offer no advantage over chemotherapy regimens.

An earlier BFM study (BFM-87) evaluated long-term outcomes with intensive chemotherapy or HSCT (for poor prognosis disease) in patients with ALL relapsing after frontline treatment (n = 207; age up to 18 years).<sup>217</sup> In this study, patients with poor prognosis included those having an 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.<sup>217</sup> The 10-year EFS rate was significantly higher among the patients who received allogeneic HSCT after second CR (n = 27) compared with those who received chemotherapy/radiotherapy only (n = 145; 59% vs. 30%; *P* = .026). All recipients of allogeneic HSCT 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 HSCT were significant independent predictors of EFS outcomes.<sup>217</sup> 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 HSCT in second CR.<sup>218</sup> 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 in this study were 30% and 36%, respectively.<sup>218</sup> 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 significantly shorter 10-year EFS (n = 76; 20%) than those who received HSCT (n = 84; 33% EFS rate;  $P < .005$ ) or the subgroup of patients who received HLA-compatible allogeneic HSCT (n = 53; 40% EFS rate;  $P < .001$ ). This EFS benefit with HSCT (or with allogeneic HSCT) 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 HSCT in this study included TBI.<sup>218</sup>

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  $<50 \times 10^9/L$ ) remained poor with no apparent advantage of HSCT, regardless of timing (eg, early or late) of bone marrow relapse.<sup>219</sup> No significant differences were observed in the EFS or OS rates between treatment with HSCT (n = 77) or chemotherapy (n = 81); the 2-year estimated EFS rates with HSCT 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.<sup>219</sup> However, data were not available on the conditioning regimen used for HSCT in this study for comparison with other trials.

It should be noted that CAR T cells are a newer strategy for treating relapsed or refractory ALL that has shown significantly greater overall survival than current regimens. CAR T cells can be used in the treatment of patients with Ph-positive or Ph-negative disease; however, the use of this regimen is restricted to clinical trials and data is not yet sufficient for incorporation into routine treatment of patients with ALL.

CAR T cells have been discussed in greater detail in an earlier section (see *Treatment of Relapsed Ph-positive ALL*).

### NCCN Recommendations for Ph-Negative ALL

#### AYA Patients (Age 15–39 Years) With Ph-Negative ALL

The panel recommends that AYA patients with Ph-negative ALL (regardless of risk group) be treated on a clinical trial, where possible. In the absence of an appropriate clinical trial, the recommended induction therapy should comprise multiagent chemotherapy regimens based on pediatric-inspired protocols, such as the CCG-1961, PETHEMA ALL-96, GRAALL-2003, and COG AALL-0434 (for T-cell ALL) regimens or the ongoing CALGB 10403 protocol. Treatment regimens should include adequate CNS prophylaxis for all patients. It is also important to adhere to the treatment regimens for a given protocol in its entirety. Testing for *TPMT* gene polymorphism should be considered for patients receiving 6-MP as part of maintenance therapy, especially in those who experience severe bone marrow toxicities.

For patients experiencing a CR following initial induction therapy, monitoring for MRD may be considered (see *NCCN Recommendations for MRD Assessment*). In these patients, continuation of the multiagent chemotherapy protocol for consolidation and maintenance would be appropriate (particularly for patients with MRD-negative remission after induction, if MRD is assessed). If a matched donor is available, consolidation with allogeneic HSCT may also be considered, particularly for patients with residual disease as assessed with MRD assays, or for those with high-risk cytogenetic features (ie, hypodiploidy, complex karyotype, or *MLL* rearrangements). The benefit of allogeneic HSCT in the setting of MRD-positive remission is currently unclear. For AYA patients experiencing less than a CR after initial induction therapy (ie, presence of primary refractory disease), the

treatment approach would be similar to that for patients with relapsed/refractory ALL.

For patients with relapsed/refractory disease after an initial CR, the approach to second-line treatment may depend on the duration of the initial response. For late relapses (ie, relapse occurring  $\geq 36$  months from initial diagnosis), re-treatment with the same induction regimen may be a reasonable option. Participation on a clinical trial is preferred, where possible. In the absence of an appropriate trial, the patient 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 HSCT if a donor is available.

#### **Adult Patients (Age $\geq 40$ Years) With Ph-Negative ALL**

For adult patients with Ph-negative ALL, the panel also recommends treatment on a clinical trial, where possible. In the absence of an appropriate clinical trial, the recommended treatment approach would initially depend on the patient's age and/or presence of comorbid conditions. Treatment regimens should include adequate CNS prophylaxis for all patients, and a given treatment protocol should be followed in its entirety, from induction therapy to consolidation/delayed intensification to maintenance therapy. Again, testing for *TPMT* gene polymorphism should be considered for patients receiving 6-MP as part of maintenance therapy, especially in those who develop severe bone marrow toxicities.

Although the age cutoff indicated in the guidelines has been set at 65 years, it should be noted that chronologic age alone is not a sufficient surrogate for defining fitness; patients should be evaluated on an individual basis to determine fitness for therapy based on factors such as performance status, end-organ function, and end-organ reserve.

For relatively fit patients (age  $< 65$  years or with no substantial comorbidities), the recommended treatment approach is similar to that for AYA patients. Induction therapy should comprise multiagent chemotherapy such as those based on protocols from the CALGB 8811 study (Larson regimen), the Linker regimen, hyper-CVAD (with or without rituximab), or the MRC UKALL XII/ECOG 2993 study. For patients experiencing a CR after initial induction therapy, monitoring for MRD may be considered (see *NCCN Recommendations for MRD Assessment*). In these patients, continuation of the multiagent chemotherapy protocol for consolidation and maintenance would be appropriate (particularly for patients with MRD-negative remission after induction, if MRD is assessed). If a matched donor is available, consolidation with allogeneic HSCT may be considered for patients with residual disease as measured by MRD assays, although the benefit of allogeneic HSCT in this setting is currently unclear. In addition, allogeneic HSCT may also be considered for relatively fit adult patients with high-risk cytogenetic features (ie, hypodiploidy, complex karyotype, or *MLL* rearrangements).

The effect of WBC counts on prognosis in adult patients with ALL is less firmly established than in pediatric populations. For adult patients experiencing less than a CR after initial induction therapy, the treatment approach would be similar to that for patients with relapsed/refractory ALL (as discussed below).

For patients who are less fit (age  $\geq 65$  years or with substantial comorbidities), the recommended induction therapy includes multiagent chemotherapy regimens or corticosteroids. Dose modifications may be required for chemotherapy agents, as needed. Patients with a CR to induction should continue consolidation with chemotherapy regimens; maintenance therapy (typically weekly methotrexate, daily 6-MP, and monthly pulses of vincristine/prednisone for 2–3 years) is

recommended. For patients with less than a CR to induction, the treatment option would be similar to that for patients with relapsed/refractory ALL.

For patients with relapsed/refractory disease after an initial CR, participation on 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 HSCT (if a donor is available) in those physically fit enough to undergo transplantation.

For recommendations on the treatment of adult patients with mature B-cell ALL, refer to the NCCN Guidelines for NHL: Burkitt Lymphoma (to view the most recent version of these guidelines, visit [NCCN.org](http://NCCN.org)).

## Evaluation and Treatment of Extramedullary Disease

### CNS Involvement in ALL

Although the presence of CNS involvement at diagnosis is uncommon (approximately 3%–7% of cases), a substantial proportion of patients (>50%) will eventually develop CNS leukemia in the absence of CNS-directed therapy.<sup>1,34</sup> CNS leukemia is defined by a WBC count of 5 leukocytes/mcL or greater in the CSF with the presence of lymphoblasts.<sup>1,34</sup> In children with ALL, CNS leukemia at diagnosis was associated with significantly decreased EFS rates.<sup>75,198,239</sup> Factors associated with increased risks for CNS leukemia in children include T-cell immunophenotype, high WBC counts at presentation, Ph-positive disease, t(4;11) translocation, and presence of leukemic cells in the CSF.<sup>81</sup> In adults with ALL, CNS leukemia at diagnosis has been associated with a significantly higher risk for CNS relapse in large trials,

although no differences were observed in 5-year EFS or DFS rates compared with subgroups without CNS leukemia at presentation.<sup>240,241</sup> CNS leukemia at diagnosis was associated with significantly decreased 5-year OS rate in one trial (29% vs. 38%;  $P = .03$ )<sup>240</sup> but not in another trial (35% vs. 31%).<sup>241</sup> Factors associated with increased risks for CNS leukemia in adults include mature B-cell immunophenotype, T-cell immunophenotype, high WBC counts at presentation, and elevated serum lactate dehydrogenase (LDH) levels.<sup>28,240</sup> CNS-directed therapy may include cranial irradiation, intrathecal chemotherapy (eg, methotrexate, cytarabine, corticosteroids), and/or high-dose systemic chemotherapy (eg, methotrexate, cytarabine, 6-MP, L-asparaginase).<sup>1,34,81</sup>

Although cranial irradiation is an effective treatment modality for CNS leukemia, it can be associated with serious adverse events, such as neurocognitive dysfunctions, secondary malignancies, and other long-term complications.<sup>1,81</sup> With the increasing use of effective intrathecal chemotherapy and high-dose systemic chemotherapy regimens, studies have examined the feasibility of eliminating cranial irradiation as part of CNS prophylaxis. In studies of children with ALL who only received intrathecal and/or intensive systemic chemotherapy for CNS prophylaxis, the 5-year cumulative incidence of isolated CNS relapse or any CNS relapse was 3% to 4% and 4% to 5%, respectively.<sup>73,198</sup> In adult patients with ALL who only received intrathecal chemotherapy and intensive systemic chemotherapy for CNS prophylaxis, the overall CNS relapse rate was 2% to 6%.<sup>83,84,242,243</sup> Therefore, with the incorporation of adequate systemic chemotherapy (eg, high-dose methotrexate and cytarabine) and intrathecal chemotherapy regimens (eg, methotrexate alone or with cytarabine and corticosteroid, which constitutes the triple intrathecal regimen), the use of upfront cranial irradiation can be avoided except in cases of overt CNS leukemia at

presentation, and the use of irradiation can be reserved for advanced disease. CNS prophylaxis is typically given throughout the course of ALL therapy starting from induction, to consolidation, to the maintenance phases of treatment.

### **NCCN Recommendations for Evaluation and Treatment of Extramedullary Involvement**

Given the risks of neurologic adverse events associated with CNS-directed therapy, comprehensive neuropsychologic testing may be useful at baseline and during posttreatment follow-up. CNS involvement should be evaluated with lumbar puncture at timing in accordance to the specific treatment protocol used for each patient. Pediatric-inspired treatment regimens typically include lumbar puncture at diagnostic workup. The panel recommends that lumbar puncture, if performed, be conducted concomitantly with initial intrathecal therapy. All patients being treated for ALL should receive adequate CNS prophylaxis with intrathecal therapy and/or systemic therapy that incorporates methotrexate.

The classification of CNS status includes the following: CNS-1 refers to no lymphoblasts in the CSF regardless of WBC count; CNS-2 is defined as a WBC count less than 5 leukocytes/mcL in the CSF with the presence of blasts; and CNS-3 is defined as a WBC count of 5 leukocytes/mcL or greater with the presence of blasts. If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic (containing  $\geq 5$  WBC/mcL in CSF with blasts), then the Steinherz-Bleyer algorithm can be used to determine the CNS classification (if the WBC/RBC ratio in the CSF is at least 2-fold greater than the WBC/RBC ratio in the blood, then the classification would be CNS-3; if not, the classification would be CNS-2).

In general, patients with CNS involvement at diagnosis (ie, CNS-3 and/or cranial nerve involvement) should receive 18 Gy of cranial irradiation. In younger AYA patients with high-risk ALL [ie, evidence of t(9;22) or BCR-ABL; t(4;11) or MLL-AF4] or T-cell ALL, use of prophylactic cranial irradiation may be an option. Notably, areas of the brain targeted by the radiation field in the management of patients with ALL are different from those targeted for brain metastases of solid tumors. In addition, patients with CNS leukemia at diagnosis should receive adequate systemic therapy, and intrathecal therapy containing methotrexate throughout the treatment course. Adequate systemic therapy should also be given in the management of patients with isolated CNS or testicular relapse.

A testicular examination should be performed for all male patients at diagnostic workup; testicular involvement is especially common among patients with T-cell ALL. Patients with clinical evidence of testicular disease at diagnosis that is not fully resolved by the end of induction therapy should be considered for radiation to the testes. Radiation therapy is typically performed concurrently with the first cycle of maintenance chemotherapy.

## **Response Assessment and Surveillance**

### **Response Criteria**

#### ***Response in Bone Marrow and Peripheral Blood***

A CR requires the absence of circulating blasts and absence of extramedullary disease (ie, no lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass, or CNS involvement). A bone marrow assessment should show trilineage hematopoiesis and fewer than 5% blasts. For a CR, absolute neutrophil counts (ANCs) should be greater than  $1.0 \times 10^9/L$  and platelet counts should be greater than  $100 \times 10^9/L$ . In addition, no recurrence should be observed for at least 4

weeks. A patient is considered to have a CR with incomplete recovery of counts (CRi) if criteria for CR are met except the ANC remains less than  $1.0 \times 10^9/L$  or the platelet count remains less than  $100 \times 10^9/L$ .

Refractory disease is defined as failure to achieve a CR at the end of induction therapy. Progressive disease is defined as an increase in the absolute number of circulating blasts (in peripheral blood) or bone marrow blasts by at least 25%, or the development of extramedullary disease. Relapsed disease is defined as the reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after achievement of a CR.

#### **Response in CNS Disease**

Remission of CNS disease is defined as achievement of CNS-1 status (no lymphoblasts in CSF regardless of WBC count) in a patient with CNS-2 (WBC count <5 leukocytes/mcL in CSF with presence of blasts) or CNS-3 (WBC count  $\geq 5$  leukocytes/mcL in CSF with presence of blasts) at diagnosis. CNS relapse is defined as development of CNS-3 status or development of clinical signs of CNS leukemia (eg, facial nerve palsy, brain/eye involvement, hypothalamic syndrome).

#### **Response in Mediastinal Disease**

A CR of mediastinal disease is defined as complete resolution of mediastinal enlargement by CT scan. An unconfirmed CR (CRu) is defined as residual mediastinal enlargement that has regressed by more than 75% in the sum of the products of the greatest perpendicular diameters (SPD). A partial response (PR) is defined as a greater than 50% decrease in the SPD of mediastinal enlargement. Progressive disease is defined as a greater than 25% increase in the SPD. No response indicates failure to meet the criteria for a PR and absence of progressive disease (as defined earlier). Relapsed mediastinal disease

is defined as recurrence of mediastinal enlargement after achievement of a CR or CRu.

Mediastinal disease is currently detected by CT scan. Although FDG-PET may also be used to detect mediastinal disease, the possibility of misinterpreting the data currently limits its use. The intense FDG uptake due to rebound hyperplasia can be misdiagnosed as lymphoma.<sup>244</sup> Until more studies are done to evaluate the use of FDG-PET in patients with ALL, it is not a recommended technique.

#### **Surveillance**

After completion of the ALL treatment regimen (including maintenance therapy), the panel recommends surveillance at regular intervals to assess disease status. During the first year after completion of therapy, patients should undergo a complete physical examination and blood tests (CBC with differential) on a monthly basis. Liver function tests should be performed every 2 months until normal values are achieved. Assessment of bone marrow aspirate, CSF, and an echocardiogram should be performed as clinically indicated; if a bone marrow aspirate is performed, comprehensive cytogenetics (including FISH), flow cytometry, and molecular tests should be considered. During the second year after completion of therapy, a physical examination (including a testicular examination for all male patients) and blood tests (CBC with differential) should be performed every 3 months. During the third year (and beyond) after completion of therapy, physical examination (including a testicular examination for all male patients) and blood tests (CBC with differential) can be performed every 6 months or as clinically indicated.

The COG has published guidelines on long-term survivorship issues for survivors of childhood cancers.<sup>245</sup> These guidelines serve as a resource for clinicians and family members/caretakers, and have the goal of

providing screening and management recommendations for late effects (eg, those that may impact growth, cognitive function, emotional concerns, reproductive health, risks for secondary malignancies, and other important health issues) that may arise during the lifetime of an AYA cancer survivor as a result of the therapeutic agents used during the course of antitumor treatment.

### 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.<sup>25,246</sup>

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  $1 \times 10^{-4}$  (<0.01%) bone marrow mononuclear cells. 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  $<1 \times 10^{-4}$  for both methods) was 97%.<sup>247</sup> The combined or tandem use of both methods would allow for MRD monitoring in all patients, thereby avoiding potential false-negative results.<sup>247,248</sup> Numerous studies in both childhood and adult ALL have shown the prognostic importance of postinduction (and/or post-consolidation) MRD measurements in predicting the likelihood of disease relapse. However, high-sensitivity PCR assays require the identification of patient-specific

markers that involve direct sequencing, and may be labor- and resource-intensive for routine application in the clinical practice setting.

### MRD Assessment in Childhood ALL

Among children with ALL who achieve 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 mononuclear cells).<sup>249,250</sup> 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 ( $P < .001$ ), which was defined based on a sensitivity level of less than  $1.5 \times 10^{-4}$  according to PCR methods.<sup>251</sup> Patients with MRD after induction also had a 10-fold increase in risk of death compared with those without detectable MRD. Moreover, the level of detectable MRD was found to be correlated 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  $1 \times 10^{-3}$ .<sup>251</sup> In another study in children with ALL (n = 158), patients with detectable MRD (measured through flow cytometry with a 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%;  $P < .001$ ).<sup>252</sup> Subsequent studies have confirmed these findings. In a study of patients (n = 165) with MRD assessment (measured through flow cytometry with a sensitivity level  $<1 \times 10^{-4}$ ) after induction therapy, the 5-year relapse rate was significantly higher among patients with MRD versus those without detectable disease (43% vs. 10%;  $P < .001$ ).<sup>250</sup> In addition, the persistence of MRD during the course of therapy was associated with risks of relapse in this study; 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 this point (68% vs. 7%;  $P = .035$ ).<sup>250</sup> MRD evaluation was shown to be a significant independent predictor of outcome in this study.

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 (in which MRD negativity was defined as  $<1 \times 10^{-4}$  through flow cytometry) by day 19 of induction therapy (about 2–3 weeks from initiation of induction); the 5-year cumulative incidence of relapse was shown to be significantly higher among patients with MRD at day 19 of treatment than those without detectable MRD (33% vs. 6%;  $P < .001$ ).<sup>249</sup> 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.<sup>253</sup> 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%;  $P < .001$ ).<sup>253</sup> Furthermore, the 5-year cumulative incidence of relapse was significantly higher among the subgroup of patients with MRD less than 0.01% (but  $\geq 0.001\%$ ) compared with those with MRD less than 0.001% or undetectable disease (13% vs. 5%;  $P < .05$ ). MRD status at the end of induction therapy was strongly correlated with MRD levels (measured by flow cytometry with 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 based on flow cytometry. Although

this study showed a higher risk of relapse among the 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, whether this lower threshold should be used to risk stratify patients or guide decisions surrounding treatment intensification is currently unknown.<sup>253</sup>

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 (measured by PCR method with sensitivity level  $\leq 0.01\%$ ) at 2 time points, days 33 and 78, which were then used to guide postinduction treatment.<sup>254</sup> 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 *TEL-AML1* subtype or hyperdiploidy were either standard risk or intermediate risk based on MRD evaluation.<sup>254</sup> The 5-year EFS rate was 92% for patients categorized as having standard-risk ( $n = 1348$ ), 78% for intermediate-risk ( $n = 1647$ ), and 50% for high-risk disease ( $n = 189$ ;  $P < .001$ ); the 5-year OS rates were 98%, 93%, and 60%, respectively. MRD-based risk stratification was able to significantly differentiate risks for relapse (between standard- and intermediate-risk subgroups) even among patient populations with *TEL-AML1* or hyperdiploidy. Importantly, in this large scale study, MRD remained a significant and powerful independent prognostic factor for relapse in the overall population.<sup>254</sup>

Several studies have suggested that an 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.<sup>255,256</sup>

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.

Approximately 20% of children treated with intensive therapies for ALL will ultimately experience disease relapse.<sup>257</sup> MRD assessment may also play a prognostic role in the management of patients in the relapsed setting.<sup>258,259</sup> In patients (n = 35) who experienced a second remission (morphologic CR) after reinduction treatment, MRD (measured by flow cytometry with 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% ( $P = .008$ ).<sup>258</sup> 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.<sup>258</sup> In another study, MRD (measured by PCR with 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.<sup>259</sup> 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 ( $P < .05$ ).<sup>259</sup> 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.

### **MRD Assessment in Adult ALL**

Studies in adults with ALL have also shown the strong correlation between MRD and risk for relapse, and the prognostic significance of MRD measurements during and after initial induction therapy.<sup>246,260-263</sup> In an analysis of postinduction MRD (measured by flow cytometry with 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;  $P = .001$ ).<sup>263</sup> 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 (at day 14, during induction therapy) remained relapse-free at 5 years.<sup>263</sup> MRD after induction therapy was also found to be significantly predictive of relapse in a subgroup analysis from the MRC UKALL/ECOG study of patients with Ph-negative B-cell lineage ALL (n = 161). 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%;  $P = .0002$ ).<sup>262</sup>

Postinduction MRD has been shown to serve as a significant independent predictor of relapse even among adult patients considered to be at standard risk based on traditional prognostic factors. In a study of adult patients with Ph-negative ALL (n = 116 evaluable), MRD status after induction therapy (measured by flow cytometry with sensitivity level <0.1%) was significantly predictive of relapse regardless of whether the patient was considered at standard risk or high risk at initial

evaluation.<sup>261</sup> Among the patients who were initially classified as having 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 that had higher levels of MRD (9% vs. 71%;  $P = .001$ ). Interestingly, MRD measured during the postconsolidation time point was not significantly predictive of outcomes.<sup>261</sup> In a study by the German Multicenter ALL (GMALL) Study Group, patients with standard-risk disease ( $n = 148$  evaluable) were monitored for MRD (measured by PCR with sensitivity level  $<0.01\%$ ) at various time points during the first year of treatment (GMALL 06/99 study).<sup>260</sup> 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  $30 \times 10^9/L$  for B-cell lineage ALL or less than  $100 \times 10^9/L$  for T-cell lineage ALL; age 15 to 65 years; and achievement of morphologic CR after phase I of induction treatment. At the end of initial induction therapy (at 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%.<sup>260</sup> 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 end points). Patients in the high-risk group (23%) had MRD of 0.01% or greater persisting through week 16, and had 3-year DFS and OS rates of only 6% and 45%, respectively. All other patients (67%) were categorized as having intermediate risk, and had 3-year DFS and OS rates of 53% and 70%, respectively.<sup>260</sup> 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 study) evaluated outcomes by MRD status

in adult patients with Ph-negative ALL.<sup>264</sup> Among the patients who achieved a CR after induction/consolidation ( $n = 39$ ), those who were MRD negative ( $<0.1\%$ ) after induction had significantly higher 3-year DFS (69% vs. 31%;  $P = .004$ ) compared with patients who were MRD positive; 3-year OS was also 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 (using a cut off of 35 years, the median age in this analysis) 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.<sup>264</sup> 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 also been shown to have prognostic significance, offering the possibility to adjust postconsolidation treatment approaches. In a study that evaluated MRD (measured by PCR with 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 HSCT after high-dose therapy.<sup>265</sup> 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%;  $P = .001$ ); similarly, the 5-year OS rate was significantly higher for patients with MRD-negative status postconsolidation (75% vs. 33%;  $P = .001$ ).<sup>265</sup> In a follow-up to the GMALL 06/99 study mentioned earlier, patients with standard-risk ALL (as defined by Bruggemann et al.<sup>260</sup>) who

experienced MRD negativity (<0.01% leukemic cells based on PCR measurements) during the first year of treatment underwent sequential MRD monitoring during maintenance therapy and follow-up.<sup>266</sup> 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.<sup>266</sup> 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 even shorter, at 4 months.<sup>266</sup> This study showed that 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 HSCT) 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  $\geq 0.01\%$ ).<sup>267</sup> 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 HSCT in clinical CR (n = 57) showed significantly higher 5-year continuous CR

(66% vs. 12%;  $P < .0001$ ) and trend for higher OS (54% vs. 33%;  $P = .06$ ) compared with the subgroup without HSCT (n = 63).<sup>267</sup> In this latter subgroup of patients with both disease that did not result in a molecular CR and who did not undergo HSCT, the median time from MRD detection to clinical relapse was approximately 8 months.<sup>267</sup> This analysis showed that MRD status following 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 HSCT.

Studies in children and adult patients with ALL suggest that differences may exist in the kinetics of leukemic cell eradication between these patient populations. Among children treated on contemporary regimens, 60% to 75% experienced clearance of MRD (by sensitive flow cytometry or PCR assays) at the end of induction therapy (typically corresponding to 5–6 weeks after initiation of induction).<sup>249-253,268</sup> In one study, nearly 50% of children had MRD clearance (<0.01% by flow cytometry) at day 19 of induction therapy.<sup>249</sup> 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.<sup>260,263</sup> Approximately 50% of cases remained MRD-positive at 2 months after initiation of induction, with further reductions in proportion of MRD-positive cases occurring beyond 3 to 5 months.<sup>246,260</sup> 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 risks for relapse in patients with ALL, and the potential role of

MRD monitoring in identifying subgroups of patients who may benefit from further intensified therapies or alternative treatment strategies. As previously discussed, current flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of fewer than  $1 \times 10^{-4}$  (<0.01%) bone marrow mononuclear cells (MNCs).<sup>269,270</sup> 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 on 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.<sup>269</sup> 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 reference laboratories that have expertise in MRD assays.

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, if MRD is being evaluated, 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 specific 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  $1 \times 10^6$  MNCs are required for analysis ( $\approx 2$  mL of bone marrow or 5–10 mL of peripheral blood provide a sufficient number of cells for multiple

analysis).<sup>269,270</sup> For MRD evaluation with the real-time quantitative PCR (RQ-PCR) assay, sampling of bone marrow MNC is preferred. At least  $1 \times 10^7$  MNCs are required for initial marker characterization and generation of individual dilution series;  $1 \times 10^6$  MNCs are sufficient for follow-up analysis.<sup>269</sup> The minimal limit of assay sensitivity (to declare MRD negativity) should be less than  $1 \times 10^{-4}$  (<0.01%).

### Supportive Care for Patients With ALL

Given the highly complex and intensive treatment protocols used in the management of ALL, supportive care issues are important considerations to ensure that patients derive the most benefit from ALL therapy. Although differences may exist between institutional standards and practices, supportive care measures for patients with ALL generally include the use of antiemetics for prevention of nausea and vomiting, blood product transfusions or cytokine support for severe cytopenias, nutritional support for prevention of weight loss, gastroenterology support, pain management, prevention and management of infectious complications, and prophylaxis for TLS. In addition, both short- and long-term consequences of potential toxicities associated with specific agents used in ALL regimens should be considered, such as with steroids (eg, risks for hyperglycemia or peptic ulcerations in the acute setting; risks for osteonecrosis or avascular necrosis with long-term use) and asparaginase (eg, risks for hypersensitivity reactions, hyperglycemia, coagulopathy, hepatotoxicity, and/or pancreatitis). Supportive care measures should be tailored to meet the individual needs of each patient based on factors such as age, performance status, extent of cytopenias before and during therapy, risks for infectious complications, disease status, and the specific agents used in the ALL treatment regimen.

### NCCN Recommendations for Supportive Care

Most chemotherapy regimens used in ALL contain agents that are at least moderately emetogenic, which may necessitate antiemetic support before initiating emetogenic chemotherapy. Antiemesis prophylaxis may include the use of agents such as serotonin receptor antagonists, corticosteroids, and/or neurokinin-1–receptor antagonists. Recommendations for antiemetic support for patients receiving chemotherapy are available in the NCCN Guidelines for Antiemesis (to view the most recent version of these guidelines, visit [NCCN.org](#)). For patients with ALL, the routine use of corticosteroids as part of antiemetic therapy should be avoided given that steroids constitute a major component of ALL regimens. For patients experiencing greater than 10% weight loss, enteral or parenteral nutritional support should be considered. Regimens to maintain bowel movement and prevent the occurrence of constipation may need to be considered for some patients. Daily doses of docusate sodium may be useful, and laxatives should be administered promptly when symptoms arise.

For patients requiring transfusion support for severe or prolonged cytopenias, only irradiated blood products should be used. Growth factor support is recommended during blocks of myelosuppressive therapy or as directed by the treatment protocol being followed for individual patients.

Patients with ALL undergoing intensive chemotherapy or allogeneic HSCT are highly susceptible to infections. Immunosuppression caused by the underlying disease and therapeutic regimens can predispose patients to common bacterial and viral infections, and to various opportunistic infections (eg, candidiasis, invasive mold infections, *Pneumocystis jirovecii*, cytomegalovirus reactivation and infection), particularly during periods of prolonged neutropenia. Patients with ALL

should be closely monitored for any signs or symptoms of infections. Cases of febrile neutropenia should be managed promptly with empiric anti-infectives and inpatient admission. Recommendations for the prevention and management of infections in patients with cancer are available via the NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections (for the most recent version of these guidelines, visit [NCCN.org](#)). For patients with ALL, antibacterial prophylaxis with a fluoroquinolone (levofloxacin is preferred) should be considered in those with expected duration of neutropenia (ANC <1000/mcL) of more than 7 days. Antiviral prophylaxis (acyclovir, valacyclovir, or famciclovir) is recommended in herpes simplex virus (HSV)–seropositive patients receiving induction/consolidation chemotherapy, and during neutropenia, and at least 30 days after allogeneic HSCT. A longer period of prophylaxis may need to be considered in allogeneic HSCT recipients with graft-versus-host disease (GVHD) or with frequent HSV reactivations before transplantation. In addition, varicella zoster virus (VZV) prophylaxis with acyclovir during the 12-month period after allogeneic HSCT may be recommended in patients who are VZV-seropositive pretransplant; agents used for HSV prophylaxis are generally also active against VZV. For allogeneic HSCT candidates who are seropositive for hepatitis B virus (HBV; hepatitis B surface antigen positive and/or hepatitis B core antibody positive), HBV prophylaxis (eg, lamivudine, adefovir) should be considered until at least 6 to 12 months after HSCT and during periods of GVHD (see the NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections). Antifungal prophylaxis with fluconazole (category 2A) or amphotericin B agents (category 2B) should be considered for all patients with ALL treated with chemotherapy. If an amphotericin B product is used for antifungal prophylaxis, a lipid formulation is generally preferred because of less infusional and renal toxicity compared with conventional amphotericin

B. Antifungal prophylaxis with posaconazole, itraconazole, and voriconazole should be avoided in patients receiving vinca alkaloids (eg, vincristine, which is included as a component of nearly all treatment regimens for ALL) because of the potential of these azoles to inhibit the cytochrome P450 3A4 isoenzyme, potentially reducing clearance of vinca alkaloids. Fluconazole prophylaxis has been shown to be effective in controlling yeast colonization and decreasing the rate of mucosal candidiasis and invasive *Candida* infections in patients receiving allogeneic HSCT.<sup>271-273</sup> For patients undergoing allogeneic HSCT, antifungal prophylaxis with fluconazole or micafungin (both category 1) should be considered until at least day 75 after HSCT; other azoles or amphotericin B agents in this setting are considered category 2B recommendations (see the NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections; for the most recent version of these guidelines, visit [NCCN.org](#)). Trimethoprim/sulfamethoxazole (TMP-SMX) for *P jirovecii* prophylaxis is effective in preventing *Pneumocystis* pneumonia in patients with acute leukemias,<sup>274,275</sup> and should be considered for all patients receiving chemotherapy for ALL. Clinicians should be aware of potential drug interactions when using TMP-SMX, as this agent can increase systemic exposure to methotrexate (due to decrease in renal clearance), thereby increasing the risks for myelotoxicity with methotrexate.<sup>276,277</sup> High doses of methotrexate can result in toxic plasma methotrexate concentrations (>10 microM/L beyond 42-48 hours) in patients with delayed methotrexate clearance. While this is more commonly seen in osteosarcoma and soft tissue tumors due to the higher dose of methotrexate in treatment, the FDA has approved the use of glucarpidase as a rescue product in patients with ALL. Leucovorin should also be given as part of the treatment of methotrexate toxicity (see *Supportive Care* on page ALL-B). Cytomegalovirus (CMV) monitoring and preemptive anti-CMV therapy

with intravenous ganciclovir, oral valganciclovir, or intravenous foscarnet should be considered for all patients; in particular, routine CMV monitoring and preemptive therapy is strongly recommended for patients undergoing allogeneic HSCT until at least 6 months after transplantation. Additional CMV surveillance should be strongly considered during chronic GVHD requiring immunosuppressive therapy and until the CD4-positive count is 100/mcL or greater (see the NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections; available at [NCCN.org](#)). It is important to note that the local susceptibility and resistance patterns of pathogens must be considered in the choice of anti-infective agents used for the prevention or treatment of infections.

Patients with ALL may be at high risk for developing acute TLS, particularly those with highly elevated WBC counts before induction chemotherapy. TLS is characterized by metabolic abnormalities stemming from the sudden release of intracellular contents into the peripheral blood because of cellular disintegration induced by chemotherapy. If left untreated, TLS can result in profound metabolic changes leading to cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and even death. Recommendations for the management of TLS are available in the “Tumor Lysis Syndrome” section of the NCCN Guidelines for NHL (available at [NCCN.org](#)). Standard prophylaxis for TLS includes hydration with diuresis, alkalinization of the urine, and treatment with allopurinol or rasburicase. Rasburicase should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, or evidence of impaired renal function. Although relatively uncommon in patients with ALL, symptomatic hyperleukocytosis (leukostasis) constitutes a medical emergency and requires immediate treatment, as recommended in the NCCN Guidelines for Acute Myeloid Leukemia (available at [NCCN.org](#)).

Leukostasis is characterized by highly elevated WBC count (usually  $>100 \times 10^9/L$ ) and symptoms of decreased tissue perfusion that often affect respiratory and CNS function. Although leukapheresis is not typically recommended in the routine management of patients with high WBC counts, it can be considered with caution in cases of leukostasis that is unresponsive to other interventions.

Key components of the ALL treatment regimen, such as corticosteroids and asparaginase, are associated with unique toxicities that require close monitoring and management. Corticosteroids, such as prednisone and dexamethasone, constitute a core component of nearly all ALL induction regimens, and are also frequently incorporated into consolidation and/or maintenance regimens. Acute side effects of steroids may include hyperglycemia and steroid-induced diabetes mellitus. Patients should be monitored for glucose control using the Insulin Sliding Scale (ISS) to minimize the risks for developing infectious complications. Another acute side effect of steroid therapy includes peptic ulceration and dyspeptic symptoms; the use of histamine-2 receptor antagonists or proton pump inhibitors is recommended during steroid therapy to reduce these risks. Although uncommon, the use of high-dose corticosteroids can be associated with mood alterations, psychosis, and other neuropsychiatric complications in patients with malignancies;<sup>278-281</sup> dose reductions may be required in these situations. A potential long-term side effect associated with steroid therapy includes osteonecrosis/avascular necrosis.

Osteonecrosis most often affects weight-bearing joints, such as the hip and/or knee, and seems to have a higher incidence among adolescents (presumably because of the period of skeletal growth) than younger children or adults.<sup>282-287</sup> In children and adolescents (age 1–21 years) with ALL evaluated in large studies of the CCG, the cumulative incidence of symptomatic osteonecrosis increased with age, from

approximately 1% in patients younger than 10 years, between 10% to 13.5% in patients between the ages of 10 and 15 years, and between 18% to 20% in patients aged 16 years and older.<sup>283,284</sup> In the Total XV study in children with ALL, symptomatic osteonecrosis occurred in 18% of patients, with most cases occurring within 1 year of treatment initiation.<sup>282</sup> Older children (age  $>10$  years) had a significantly higher cumulative incidence of osteonecrosis (45% vs. 10%;  $P < .001$ ) compared with younger children (age  $\leq 10$  years). In this study, factors such as older age, lower serum albumin levels, higher serum lipid levels and higher exposure to dexamethasone were associated with risks for osteonecrosis. Moreover, higher plasma exposure to dexamethasone (as measured by area under the concentration curve at Week 8 of therapy) and lower serum albumin were significant factors associated with the development of severe (grade 3 or 4) osteonecrosis, even after adjusting for age and treatment arm.<sup>282</sup> In a recent DFCI ALL Consortium study in children and adolescents that included randomization to postinduction therapy with dexamethasone versus prednisone, dexamethasone was associated with a significantly increased 5-year EFS but, in older children, the increased cumulative incidence of osteonecrosis was comparable with prednisone.<sup>287</sup> An earlier CCG study (CCG-1882) had reported a higher incidence of symptomatic osteonecrosis among children randomized to receive an augmented ALL regimen with 2 courses of dexamethasone compared with those who received 1 course (23% vs. 16%;  $P =$  not significant).<sup>284</sup> These studies appeared to suggest that dexamethasone, particularly in higher doses, may be associated with increased risks for osteonecrosis in older children and adolescents. To further investigate these findings, the recent CCG-1961 trial randomized patients ( $n = 2056$ ; age 1–21 years) to postinduction intensification treatment with intermittent dose scheduling of dexamethasone (10 mg/m<sup>2</sup> daily on days 0–6 and days 14–20) versus continuous doses of dexamethasone (10 mg/m<sup>2</sup> daily on

days 0–20).<sup>283</sup> Among older children and adolescents (age ≥10 years) who had rapid response to induction, use of intermittent dexamethasone during intensification phase was associated with significantly decreased incidence of osteonecrosis compared with the standard continuous dose of dexamethasone (9% vs. 17%;  $P = .0005$ ). The difference was particularly pronounced among adolescent patients 16 years and older (11% vs. 37.5%, respectively;  $P = .0003$ ). This randomized trial suggested that the use of intermittent (alternative week) dexamethasone during intensification phases may reduce the risks of osteonecrosis in adolescents.<sup>283</sup> To monitor patients for risks of developing symptomatic osteonecrosis, routine measurements for vitamin D and calcium levels should be obtained, and periodic radiographic evaluation (using plain films or MRI) should be considered.

Asparaginase is also a core component of ALL regimens, most often given during induction and consolidation for Ph-negative disease. Three different formulations of the enzyme have been approved by the FDA, native *Escherichia coli* (*E coli*)-derived asparaginase (*E coli* asparaginase); asparaginase derived from *E coli* that has been modified with a covalent linkage to polyethylene glycol (pegasparaginase); and asparaginase derived from a different Gram-negative bacteria *Erwinia chrysanthemi* (*Erwinia* asparaginase). These formulations differ in their pharmacologic properties, and may also differ in terms of immunogenicity.<sup>288-290</sup> Regardless of the formulation, asparaginase can be associated with potentially severe hypersensitivity reactions (including anaphylaxis) arising from the production of anti-asparaginase antibodies. Pegasparaginase seems to be associated with a lower incidence of neutralizing antibodies compared with native asparaginase.<sup>291</sup> However, cross-reactivity between neutralizing antibodies against native *E coli* asparaginase and pegasparaginase has been reported.<sup>292,293</sup> Moreover, a recent study showed that high

anti-asparaginase antibody level after initial therapy with native *E coli* asparaginase was associated with decreased asparaginase activity during subsequent therapy with pegasparaginase.<sup>294</sup> In contrast, no cross-reactivity between antibodies against native *E coli* asparaginase and *Erwinia* asparaginase was reported,<sup>292,293</sup> and enzyme activity of *Erwinia* asparaginase was not affected by the presence of anti-*E coli* asparaginase antibodies.<sup>294</sup> A study from the DFCI ALL Consortium showed the feasibility and activity of using *Erwinia* asparaginase in pediatric and adolescent patients who developed hypersensitivity reactions to *E coli* asparaginase during frontline therapy; importantly, treatment with *Erwinia* asparaginase did not negatively impact EFS outcomes in these patients.<sup>295</sup>

Native *E coli* asparaginase is no longer available; therefore, the NCCN panel recommends the use of pegasparaginase in the treatment of patients with ALL. For patients who develop severe hypersensitivity reactions during treatment with pegasparaginase, *Erwinia* asparaginase should be substituted (see *Supportive Care: Asparaginase Toxicity Management*). *Erwinia* asparaginase is currently approved by the FDA for patients with ALL who have developed hypersensitivity to *E coli*-derived asparaginase.<sup>296</sup> Asparaginase can be associated with various toxicities, including pancreatitis (eg, ranging from asymptomatic cases with amylase or lipase elevation, to symptomatic cases with vomiting or severe abdominal pain), hepatotoxicity (eg, increase in alanine or glutamine aminotransferase), and coagulopathy (eg, thrombosis, hemorrhage). Detailed recommendations for the management of asparaginase toxicity in AYA and adult patients were published,<sup>290</sup> and have been incorporated into the NCCN Guidelines for ALL (see “Supportive Care: Asparaginase Toxicity Management”).

## References

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